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Two phase 3, multicenter, randomized, placebo-controlled clinical trials of fampridine-SR for treatment of spasticity in chronic spinal cord injury.

D. D. Cardenas
University of Miami

J. F. Ditunno
Thomas Jefferson University

V. Graziani
Thomas Jefferson University

A. B. McLain
University of Alabama at Birmingham

P. Lammertse
Craig Hospital

See next page for additional authors

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ORIGINAL ARTICLE

Two phase 3, multicenter, randomized, placebo-controlled clinical trials of fampridine-SR for treatment of spasticity in chronic spinal cord injury

DD Cardenas[1], JF Ditunno[2], V Graziani[3], AB McLain[4], DP Lammertse[5], PJ Potter[6], MS Alexander[7], R Cohen[8] and AR Blight[8]

Study design: Two randomized, double-blind, placebo-controlled trials.
Objective: To evaluate the efficacy and safety of fampridine sustained-release tablets (fampridine-SR) 25 mg twice daily for moderate-to-severe spasticity in patients with chronic spinal cord injury (SCI).
Setting: United States and Canada.
Methods: Patients with incomplete chronic SCI were randomized to twice daily fampridine-SR 25 mg or placebo, with a 2-week single-blind placebo run-in, a 2-week titration, 12 weeks of stable dosing, 2 weeks of downward titration and 2 weeks of untreated follow-up. Co-primary end points were the change from baseline, averaged over the double-blind treatment period, for Ashworth score (bilateral knee flexors and extensors) and a 7-point Subject Global Impression of treatment (SGI; 1, terrible; 7, delighted). Secondary end points were: Penn Spasm Frequency Scale; the motor/sensory score from the International Standards for Neurological Classification of SCI; Clinician's Global Impression of Change of neurological status; and the International Index of Erectile Function (men) or the Female Sexual Function Index (women).
Results: The populations were 212 and 203 patients in the two studies, respectively. Changes from baseline in Ashworth score were −0.15 (placebo) and −0.19 (fampridine-SR) in the first study, and −0.16 (placebo) and −0.28 (fampridine-SR) in the second study. The between-treatment difference was not significant for either the Ashworth score or the SGI and, with few exceptions, neither were the secondary end points. Fampridine-SR was generally well tolerated; treatment-emergent adverse events (TEAEs) and serious TEAEs were reported with similar frequency between treatments.
Conclusion: Fampridine-SR was well tolerated. No significant differences were observed between treatment groups for the primary end points of Ashworth score and SGI.
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Keywords: fampridine; dalfampridine; 4-aminopyridine; spasticity; sexual function; spinal cord injuries

INTRODUCTION

The concept of potassium channel blockade to improve conduction in demyelinated nerve fibers has been pursued for over 30 years, primarily with 4-aminopyridine. Animal studies indicate that 4-aminopyridine acts through restoration of action potential conduction in damaged nerve fibers, although it may also enhance synaptic transmission and neuronal excitability.[1,2] At concentrations of 1–10 mM, 4-aminopyridine broadly blocks voltage-dependent potassium channels, but its 50% inhibitory concentration values vary over orders of magnitude across channel types.[3] Few laboratory studies demonstrated effects of 4-aminopyridine on potassium channels at the submicromolar concentrations seen in human plasma following clinically practical doses.[4] This concentration dependence probably explains its clinical effects in demyelinating conditions without significant effects on cardiac function and little or no effect on normal neurological function in most individuals.[5]

Several names have been used for 4-aminopyridine, including its previous United States Adopted Name and current International Nonproprietary Name of 'fampridine'. At the time of the studies described here, the 'sustained release' (SR) tablet formulation was known by the provisional name 'Fampridine-SR'. This same formulation, at a dose of 10 mg to be taken approximately every 12 h, was approved by the United States Food and Drug Administration to improve walking in people with multiple sclerosis based on studies showing an increase in walking speed.[6] The United States Adopted Name was changed to 'dalfampridine' to avoid potential name confusion and the formulation is referred to as 'extended release.' In Europe, the same formulation is known as 'fampridine

[1]Department of Rehabilitation Medicine, University of Miami, Miami, FL, USA; [2]Department of Rehabilitation Medicine, Thomas Jefferson University, Philadelphia, PA, USA; [3]Department of Rehabilitation Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, USA; [4]Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham, Birmingham, AL, USA; [5]Research Department, Craig Hospital, Englewood, CO, USA; [6]Department of Physical Medicine and Rehabilitation, Parkwood Hospital, St Joseph's Health Care, London, Ontario, Canada; [7]Department of Physical Medicine and Rehabilitation, Veterans Affairs Medical Center, Birmingham, AL, USA and [8]Acorda Therapeutics, Inc., Ardsley, NY, USA
Correspondence: Dr DD Cardenas, South Florida Spinal Cord Injury Model System, Department of Rehabilitation Medicine, University of Miami, Miller School of Medicine, 1120 NW 14th Street, Suite 958, Miami, FL 33136, USA.
E-mail: DCardenas@med.miami.edu
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prolonged-release', although the terminology varies in other parts of the world. In this paper, the formulation is referred to by the name used at the time of the studies, 'fampridine-SR' and the active drug by its chemical name, 4-aminopyridine, with respect to laboratory studies.

Several studies of fampridine that evaluated the effects on neurological outcomes, including spasticity, in chronic spinal cord injury (SCI) showed encouraging but mixed results.[7–10] Spasticity, one of the most common symptoms of SCI, affects patient function and quality of life.[11] The currently approved treatments are limited by adverse effects and often require dosing as frequently as every 4 h.[12] Measuring spasticity can be difficult because of variability in severity over time, and the mix of hyperreflexia and muscle spasms.

In a phase 2 trial that compared 25 and 40 mg doses of fampridine-SR against placebo, the 25 mg dose exhibited equivalent or better efficacy for the primary end point of spasticity with better safety and tolerability profiles as compared with the 40 mg dose.[13] In addition, some improvements with 25 mg fampridine-SR were observed relative to placebo on secondary measures of bladder, bowel and sexual functions. The two studies reported here evaluated the efficacy and safety of fampridine-SR, 25 mg twice daily, for the treatment of moderate-to-severe spasticity in patients with chronic, incomplete SCI, regardless of concomitant treatment with other antispasmodic medications.

MATERIALS AND METHODS

Study designs

Studies SCI-F301 and SCI-F302, of identical double-blind, placebo-controlled design, were conducted at 45 and 33 centers, respectively, in the United States and Canada; SCI-F301 was conducted from July 2002 to February 2004, and SCI-F302 was conducted between June 2002 and November 2003. Both studies received approval from Institutional Review Boards or ethics committees, and were performed in accordance with the revised Declaration of Helsinki; all patients or their legal representatives provided written informed consent.

Both studies consisted of a 2-week, single-blind placebo run-in, a 2-week titration, 12 weeks of stable dosing, 2-week downward titration and 2 weeks of untreated follow-up. Patients were randomized to fampridine-SR 25 mg or placebo, twice daily, with treatment groups stratified by concomitant antispasmodic medication use to ensure that both groups included approximately equal proportions of patients using these medications. Patients undergoing physical therapy were permitted to continue their sessions during the study only if there were no changes in the frequency of sessions or the methods used.

Patient populations

Men and women 18 to 70 years old were required to have chronic, incomplete, traumatic SCI between C3 and T10 inclusive, defined as having occurred $\geqslant$18 months before screening; stable neurological status for $\geqslant$6 months; and American Spinal Injury Association (ASIA) Impairment Scale (AIS) classification grade B, C or D. Additional inclusion criteria were the presence of deep tendon reflexes at the knees and bulbocavernosus or anal wink reflex; clinically significant spasticity of the lower extremities, with average Ashworth Score of $>$2.0 on a scale of 1–5 (1, no increase in tone; 5, affected parts rigid in flexion or extension) across the four muscle groups tested. Key exclusion criteria were history of seizure; infection at screening; history of chronic urinary tract infections; allergy to pyridine or tablet excipients; clinically significant abnormal laboratory values or electrocardiogram at screening; injection with botulinum toxin within 4 months of screening or with phenol or alcohol within 12 months; and previous treatment with any 4-aminopyridine formulation. Women were excluded if they were pregnant, lactating or of childbearing potential and not using adequate birth control.

Efficacy end points

Efficacy was based on two co-primary end points: the change from baseline in Ashworth score, averaged over the bilateral knee flexors and extensors, and a 7-point Subject Global Impression of treatment (SGI; 1, terrible; 7, delighted), averaged over double-blind treatment. Baseline scores were the average of values at the 1- and 2-week time points of the placebo run-in.

Secondary end points included the Penn Spasm Frequency Scale;[14] the motor/sensory score from the International Standards for Neurological Classification of Spinal Cord Injury;[15] Clinician's Global Impression of Change (CGI-C) of the patient's neurological status, using a 7-point scale (1, very much improved; 7, very much worse); and the International Index of Erectile Function (IIEF)[16] for men or the Female Sexual Function Index[17] for women. Bowel and bladder function outcomes were collected in response to specific questions as part of a daily patient diary questionnaire using an interactive voice response system. Questions included the number of times per day the patient experienced accidental urination/leakage, the number of bowel movements per day and the number of minutes per day spent on bowel routine.

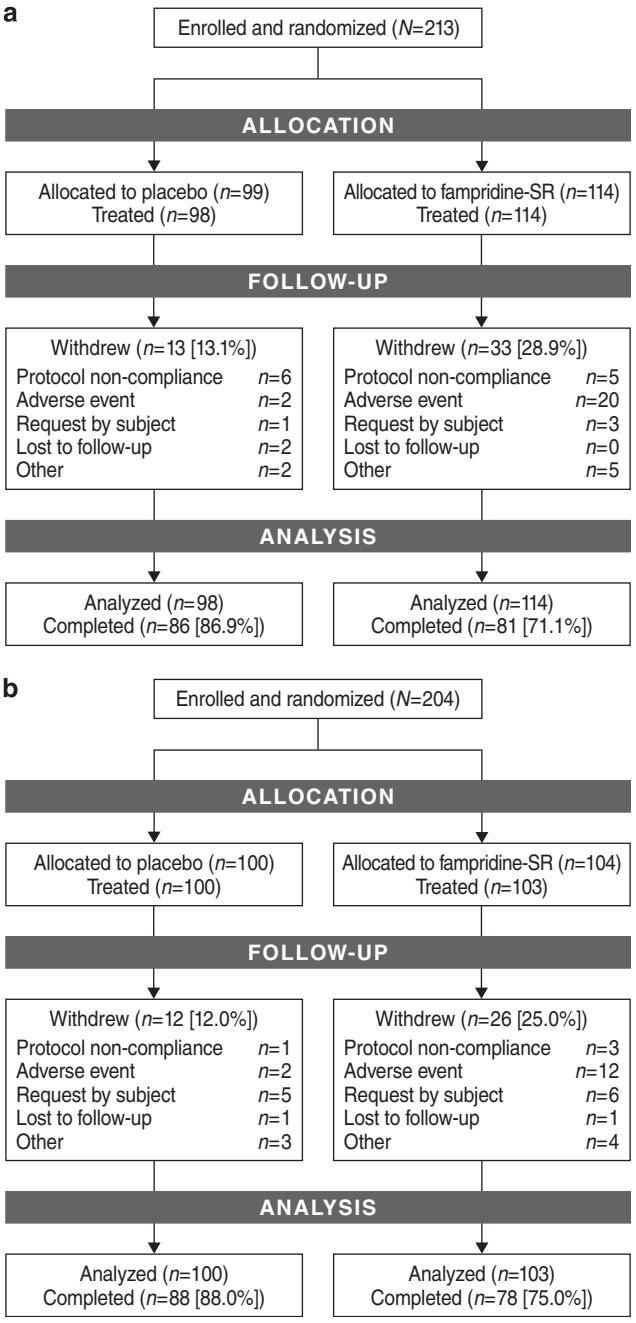

Figure 1 Disposition of patients in studies (**a**) SCI-F301 and (**b**) SCI-F302.

Safety and tolerability evaluation

The safety population was defined as all randomized patients who received ⩾1 dose of investigational drug. Evaluation of safety and tolerability was based on the incidence and severity of treatment-emergent adverse events (TEAEs) and changes in vital signs, laboratory values, electrocardiographic evaluation and physical examination findings. TEAEs were any events during double-blind treatment and up to 14 days after the last dose of investigational drug.

Statistical analysis

The modified intent-to-treat population, defined as all randomized patients with ⩾1 efficacy evaluation during double-blind treatment, was used for all efficacy analyses, with last observation carried forward for imputation of missing values. Between-treatment comparisons for all efficacy end points except CGI-C were performed using an analysis of covariance model with treatment, center and concomitant medication (use of antispasmodic drugs, yes/no) as the main effects, and baseline as a covariate. Assessments of bladder, bowel and sexual functions were secondary end points, although the studies were not powered for these end points. Analysis of variance with treatment, center and use of antispasmodic drug as the main effects was used for CGI-C.

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

RESULTS

Study populations

In SCI-F301, 213 patients (99 placebo, 114 fampridine-SR) were randomized, and in SCI-F302, 204 patients (100 placebo, 104 fampridine-SR) were randomized. Of these patients, 86.9 and 71.1% of the placebo- and fampridine-treated patients completed SCI-F301 (Figure 1a); 88.0 and 75.0% of the respective groups completed SCI-F302 (Figure 1b). The modified intent-to-treat populations consisted of 212 and 203 patients from SCI-F301 and SCI-F302, respectively; one placebo patient in SCI-F301 and one fampridine-SR patient in SCI-F302 did not take any investigational drug, and they were excluded from the analysis.

Demographic and clinical characteristics were balanced between groups in each study except for a significantly higher score on the ASIA Total Pin Prick subscore in the fampridine-SR group in SCI-F302 (Table 1). Subjects were primarily male (84–88%) and Caucasian (83–89%), with a mean (s.d.) age of 40.9 (12.5) years in SCI-F301 and 40.9 (12.0) years in SCI-F302. Motor vehicle accidents were the primary cause of injury (40.0–49.0%), followed by falls and diving accidents.

The most frequent medications at baseline were antispasmodics (for example, baclofen, tizanidine) that were used by 68.9 and 58.6%

Table 1 Baseline demographic and clinical characteristics of the patient populations in studies SCI-F301 and SCI-F302

Variable	*SCI-F301*			*SCI-F302*		
	Placebo (n = *98*[a])	*Fampridine-SR* (n = *114*)	P-*value*	*Placebo* (n = *100*)	*Fampridine-SR* (n = *103*[b])	P-*value*
Age, years, mean ± s.d.	40.1 ± 13.1	41.6 ± 12.1	0.372	40.5 ± 12.3	41.3 ± 11.8	0.669
Gender, n *(%)*			0.830			0.620
Male	85 (86.7)	100 (87.7)		86 (86.0)	86 (83.5)	
Female	13 (13.3)	14 (12.3)		14 (14.0)	17 (16.5)	
Race, n *(%)*			0.507			0.678
Caucasian	81 (82.7)	94 (82.5)		87 (87.0)	92 (89.3)	
Black	12 (12.2)	18 (15.8)		10 (10.0)	8 (7.8)	
Asian/Pacific Islander	2 (2.0)	0		0	1 (1.0)	
American Indian/Alaskan Native	1 (1.0)	1 (0.9)		0	0	
Other	2 (2.0)	1 (0.9)		3 (3.0)	2 (1.9)	
ASIA scores, mean ± s.d.						
Total motor score	57.0 ± 25.1	53.8 ± 26.6	0.379	53.6 ± 26.2	59.1 ± 25.0	0.125
Total light touch score	78.1 ± 3.8	75.7 ± 23.0	0.460	72.5 ± 24.1	76.3 ± 21.9	0.244
Total pin prick score	68.2 ± 27.7	65.2 ± 26.9	0.427	56.6 ± 28.2	64.2 ± 26.3	0.046
ASIA Impairment Scale, n *(%)*						0.660
B	28 (28.6)	42 (36.8)	0.357	32 (32.0)	32 (31.1)	
C	32 (32.7)	29 (25.4)		30 (30.0)	26 (25.2)	
D	38 (38.8)	43 (37.7)		38 (38.0)	45 (43.7)	
Cause of injury, n *(%)*			0.587			0.368
Motor vehicle accident	48 (49.0)	49 (43.0%)		40 (40.0)	42 (40.8)	
Fall	13 (13.3)	23 (20.2%)		18 (17.5)	16 (16.0)	
Diving	13 (13.3)	10 (8.8)		16 (16.0)	16 (15.5)	
Sports	8 (8.2)	8 (7.0)		13 (13.0)	7 (6.8)	
Gunshot wound	7 (7.1)	9 (7.9)		7 (7.0)	4 (3.9)	
Other	9 (9.2)	15 (13.2)		8 (8.0)	16 (15.5)	
Special syndrome, n *(%)*			0.218			0.550
Brown-Séquard	2 (2.0)	9 (7.9)		5 (5.0)	9 (8.7)	
Anterior cord	1 (1.0)	2 (1.8)			1 (1.0)	
Mixed	1 (1.0)	0		4 (4.0)	1 (1.0)	
Other	5 (5.1)	3 (2.6)		3 (3.0)	4 (3.9)	
Use of antispasmodic medication, *n* (%)	69 (70.4)	77 (67.5)	0.653	62 (62.0)	57 (55.3)	0.335

Abbreviations: ASIA, American Spinal Injury Association; Fampridine-SR, fampridine suspended-release tablets.
[a]Although 99 patients were randomized to placebo, 1 patient in the placebo group did not take any investigational drug and was excluded from the evaluated patient population.
[b]Although 104 patients were randomized to fampridine-SR, 1 patient in the fampridine-SR group did not take any investigational drug and was excluded from the evaluated patient population.

of patients in SCI-F301 and SCI-F302, respectively (Table 1). Use of concomitant medications was similar between treatment groups and consistent between the studies, and concomitant use of baclofen was reported during double-blind treatment by 63.3% of placebo patients and 54.4% of fampridine-SR patients in SCI-F301, and by 54.0 and 47.1% in SCI-F302.

Adherence to treatment

Therapy adherence was high; 95.9% of placebo and 84.2% of fampridine-SR patients had $\geqslant$80% adherence in SCI-F301, with 94.9 and 84.5%, respectively, in SCI-F302.

Efficacy

Although improvements on the Ashworth scale in both studies were numerically better with fampridine-SR, the differences between treatment groups in change from baseline for this and the co-primary end point of SGI were small, and none of these differences achieved statistical significance (Figure 2). Only minimal changes from baseline were observed for the secondary end point of the Penn Spasm Frequency Scale (Table 2), and the only significant difference between treatments was on the Upper Extremity subscale in SCI-F302. Changes in CGI-C scores were −0.1 to −0.2 points. No significant differences were observed between treatments for the Total Motor Score in either study; adjusted changes from baseline were 1.7 for placebo and 1.2 for fampridine-SR in SCI-F301, and 0.7 and 0.4, respectively, in SCI-F302.

On sexual dysfunction measures, the only significant between-treatment differences were for a slightly greater improvement observed among men treated with fampridine-SR on two IIEF domains, erectile function ($P=0.016$) and orgasmic function ($P=0.032$) in SCI-F301 (Table 3).

No significant differences between treatments were observed for bladder and bowel function in SCI-F301, although there was a significantly greater increase with fampridine-SR relative to placebo for the number of bowel movements in SCI-F302 ($P=0.006$; Table 4).

Safety and tolerability

The incidence of TEAEs was similar between treatment groups in SCI-F301, 85.7 and 82.5% for placebo and fampridine-SR, respectively, but it was slightly higher with fampridine-SR (95.1%) relative to placebo (83.0%) in SCI-F302 (Table 5). TEAEs were generally of mild or moderate severity. Serious TEAEs were reported with a similar frequency in placebo and fampridine-SR groups in both studies (Table 5). The single death, a placebo-treated patient in SCI-F302, was caused by atherosclerotic disease complicated by morphine intoxication and was considered unrelated to treatment by the investigator.

In SCI-F301, 3 (3.1%) placebo and 19 (16.7%) fampridine-SR patients discontinued because of TEAEs (Table 5). Within the fampridine-SR group, the most common TEAEs leading to discontinuation were dizziness (6.1%) and hypertonia, insomnia and asthenia (2.6% each). Similar proportions and reasons for TEAE-related discontinuations were reported in SCI-F302; 3 (3.0%) and 16 (15.5%) patients in the placebo and fampridine-SR groups, respectively, with dizziness (3.9%), hypertonia (2.9%) and paresthesia (2.9%) the most common TEAEs leading to discontinuation for fampridine-SR.

In both studies, fampridine-SR had a higher frequency of TEAEs considered possibly or probably related to treatment relative to placebo: 43.0% vs 24.5% in SCI-F301 and 48.5% vs 25.0% in SCI-F302 (Table 5). The most common TEAEs with fampridine-SR included urinary tract infection, hypertonia, dizziness, pain and constipation (Table 5).

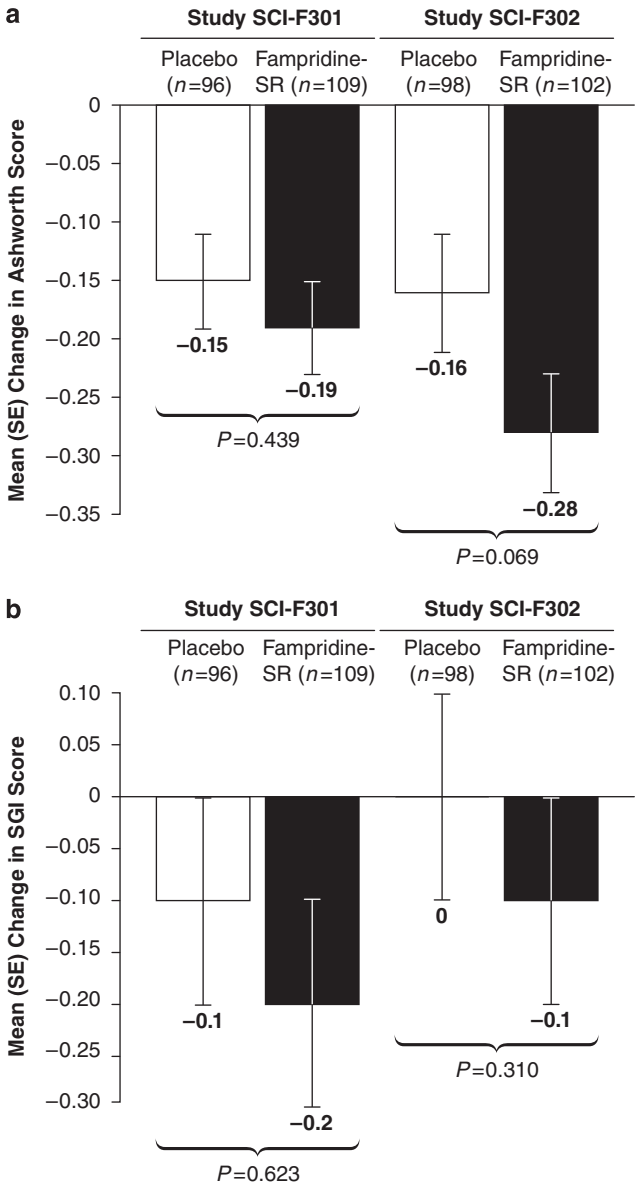

Figure 2 Adjusted change from baseline, averaged over the double-blind treatment period, for the co-primary end points of (**a**) Ashworth Spasticity Scale scores and (**b**) SGI of treatment.

Several patients in both studies had clinically significant changes in laboratory values, but no trends were observed for between-treatment differences for type or frequency of changes. Both groups had similar percentages of patients with potentially significant changes in heart rate-corrected QT values (prolongation $\geqslant$30 ms) during the study: 12.6% and 12.4% of placebo and fampridine-SR patients, respectively.

DISCUSSION

The design of these two phase 3 trials was based on the previous phase 2 trial[13] with respect to dose selection, primary outcome measures and recruitment criteria. In *post-hoc* analyses, the earlier study showed significant improvements in Ashworth score among subjects who had more than minimal spasticity at baseline. Therefore, these studies prospectively recruited individuals with an average Ashworth score of

Table 2 Adjusted change from baseline on the Penn Spasm Frequency Scale in studies SCI-F301 and SCI-F302

	SCI-F301					*SCI-F302*				
	Placebo (n = *95*)		*Fampridine-SR* (n = *107*)		P-*value*	*Placebo* (n = *98*)		*Fampridine-SR* (n = *102*)		P-*value*
	Baseline, mean ± s.d.	*Change, mean ± s.e.*	*Baseline, mean ± s.d.*	*Change, mean ± s.e.*		*Baseline, mean ± s.d.*	*Change, mean ± s.e.*	*Baseline, mean ± s.d.*	*Change, mean ± s.e.*	
Spasm frequency										
Upper extremity	0.91 ± 1.00	−0.06 ± 0.05	1.00 ± 1.08	−0.07 ± 0.04	0.821	1.11 ± 1.06	0.02 ± 0.05	0.85 ± 0.95	−0.13 ± 0.05	0.044
Lower extremity	2.24 ± 0.91	−0.02 ± 0.06	2.30 ± 1.02	−0.05 ± 0.06	0.742	2.37 ± 1.07	−0.10 ± 0.05	2.12 ± 1.04	−0.12 ± 0.05	0.859
Spasm severity										
Upper extremity	0.78 ± 0.84	−0.04 ± 0.04	0.85 ± 0.90	−0.05 ± 0.04	0.891	0.89 ± 0.83	−0.02 ± 0.04	0.75 ± 0.80	−0.09 ± 0.03	0.108
Lower extremity	2.15 ± 0.68	−0.07 ± 0.04	2.07 ± 0.67	−0.10 ± 0.04	0.693	2.08 ± 0.68	−0.07 ± 0.04	2.18 ± 0.66	−0.14 ± 0.04	0.233

Abbreviation: Fampridine-SR, fampridine suspended-release tablets.

Table 3 Adjusted change from baseline at the end of double-blind treatment for sexual function using the IIEF and the FSFI in studies SCI-F301 and SCI-F302

	Mean change ± s.e. (n)				
	SCI-F301			*SCI-F302*	
	Placebo	*Fampridine-SR*	P-*value*	*Placebo*	*Fampridine-SR*	P-*value*
IIEF						
Erectile function	−1.5 ± 0.9 (74)	1.5 ± 0.9 (71)	0.016	1.6 ± 1.0 (77)	0.8 ± 1.1 (65)	0.572
Orgasmic function	−0.7 ± 0.4 (73)	0.5 ± 0.4 (72)	0.032	0 ± 0.3 (76)	0.3 ± 0.4 (64)	0.554
Sexual desire	0.1 ± 0.2 (74)	−0.1 ± 0.2 (71)	0.669	0 ± 0.2 (75)	0 ± 0.2 (64)	0.843
Intercourse satisfaction	−0.7 ± 0.4 (74)	0.4 ± 0.4 (72)	0.058	0.4 ± 0.5 (76)	0.4 ± 0.6 (64)	0.956
Overall satisfaction	0.1 ± 0.3 (60)	0.2 ± 0.3 (62)	0.943	0.3 ± 0.2 (66)	0.4 ± 0.3 (51)	0.632
FSFI						
Desire	0.4 ± 0.3 (12)	0.7 ± 0.3 (11)	0.298	0.2 ± 0.3 (13)	0.7 ± 0.3 (14)	0.258
Arousal	0.7 ± 0.3 (12)	0.4 ± 0.4 (11)	0.496	0.2 ± 0.4 (13)	0.6 ± 0.4 (14)	0.526
Lubrication	0.7 ± 0.6 (13)	−0.1 ± 0.6 (10)	0.228	−0.2 ± 0.5 (13)	0.7 ± 0.5 (14)	0.146
Orgasm	0.6 ± 0.4 (13)	0.5 ± 0.4 (11)	0.903	0.4 ± 0.2 (13)	0.2 ± 0.2 (14)	0.308
Satisfaction	0.8 ± 0.4 (12)	0 ± 0.4 (11)	0.106	0.3 ± 0.3 (12)	0.4 ± 0.3 (13)	0.925
Pain	0.6 ± 0.7 (12)	−0.1 ± 0.8 (11)	0.483	−0.1 ± 0.5 (13)	0.7 ± 0.5 (14)	0.260

Abbreviations: Fampridine-SR, fampridine suspended-release tablets; FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function.

Table 4 Adjusted change from baseline, averaged over the double-blind treatment period, for Bladder/Bowel Function Diary Scores in studies SCI-F301 and SCI-F302

	SCI-F301					*SCI-F302*				
	Placebo (n = *97*)		*Fampridine-SR* (n = *114*)		P-*value*	*Placebo* (n = *99*)		*Fampridine-SR* (*n* = *103*)		P-*value*
	Baseline, mean ± s.d.	*Change, mean ± s.e.*	*Baseline, mean ± s.d.*	*Change, mean ± s.e.*		*Baseline, mean ± s.d.*	*Change, mean ± s.e.*	*Baseline, mean ± s.d.*	*Change, mean ± s.e.*	
Number of accidental urinations or leakages	0.7 ± 2.0	−0.1 ± 0.1	0.7 ± 2.0	0.0 ± 0.1	0.095	0.6 ± 2.3	−0.2 ± 0.2	1.4 ± 4.0	−0.2 ± 0.2	0.932
Number of bowel movements	0.7 ± 0.4	0.0 ± 0.0	0.7 ± 0.5	0.0 ± 0.0	0.082	0.7 ± 0.5	−0.0 ± 0.0	0.8 ± 0.6	0.1 ± 0.0	0.006
Number of minutes spent on bowel routine	23.8 ± 24.2	−2.7 ± 1.0	21.3 ± 18.5	−1.0 ± 0.9	0.159	19.3 ± 18.1	0.3 ± 0.93	19.2 ± 16.3	−0.7 ± 0.9	0.437

Abbreviation: fampridine-SR, fampridine suspended-release tablets.

Table 5 Incidence of TEAEs in studies SCI-F301 and SCI-F302

Adverse event	*Incidence,* n *(%)*			
	SCI-F301[a]		*SCI-F302*	
	Placebo (n = *98*)	*Fampridine-SR* (n = *114*)	*Placebo* (n = *100*)	*Fampridine-SR* (n = *103*)
Any TEAE	84 (85.7)	94 (82.5)	83 (83.0)	98 (95.1)
Serious TEAEs	6 (6.1)	6 (5.3)	9 (9.0)	8 (7.8)
Deaths	0	0	1 (1.0)	0
Discontinuation due to TEAEs	3 (3.1)	19 (16.7)	3 (3.0)	16 (15.5)
Treatment-related TEAEs[b]	24 (24.5)	49 (43.0)	25 (25.0)	50 (48.5)
Most common TEAEs[c]				
Urinary tract infection	16 (16.3)	34 (29.8)	15 (15.0)	22 (21.4)
Hypertonia	25 (25.5)	23 (20.2)	17 (17.0)	24 (23.3)
Dizziness	3 (3.1)	15 (13.2)	1 (1.0)	12 (11.7)
Pain	14 (14.3)	13 (11.4)	14 (14.0)	19 (18.4)
Constipation	8 (8.2)	11 (9.6)	10 (10.0)	19 (18.4)
Accidental injury	17 (17.3)	10 (8.8)	16 (16.0)	9 (8.7)
Headache	8 (8.2)	10 (8.8)	8 (8.0)	15 (14.6)
Nausea	4 (4.1)	10 (8.8)	6 (6.0)	9 (8.7)
Paresthesia	5 (5.1)	10 (8.8)	9 (9.0)	18 (17.5)
Insomnia	3 (3.1)	10 (8.8)	6 (6.0)	16 (15.5)
Asthenia	4 (4.1)	9 (7.9)	6 (6.0)	3 (2.9)
Back pain	6 (6.1)	9 (7.9)	3 (3.0)	10 (9.7)
Infection	10 (10.2)	9 (7.9)	15 (15.0)	11 (10.7)
Diarrhea	8 (8.2)	8 (7.0)	7 (7.0)	2 (1.9)
Dyspepsia	2 (2.0)	8 (7.0)	5 (5.0)	5 (4.9)
Nervousness	0	8 (7.0)	2 (2.0)	5 (4.9)
Arthralgia	10 (10.2)	7 (6.1)	3 (3.0)	4 (3.9)
Rash	3 (3.1)	7 (6.1)	7 (7.0)	5 (4.9)
Skin ulcer	7 (7.1)	7 (6.1)	5 (5.0)	5 (4.9)
Sweating	1 (1.0)	7 (6.1)	3 (3.0)	5 (4.9)
Anxiety	1 (1.0)	6 (5.3)	1 (1.0)	5 (4.9)
Urinary incontinence	5 (5.1)	6 (5.3)	4 (4.0)	4 (3.9)
Abdominal pain	4 (4.1)	5 (4.4)	5 (5.0)	10 (9.7)
Peripheral edema	2 (2.0)	3 (2.6)	9 (9.0)	7 (6.8)
Fever	2 (2.0)	5 (4.4)	5 (5.0)	6 (5.8)
Pharyngitis	—	—	6 (6.0)	6 (5.8)

Abbreviations: Fampridine-SR, fampridine suspended-release tablets; TEAE, treatment-emergent adverse event.
[a]TEAEs include adverse events during double-blind treatment and up to 14 days after the last dose of investigational drug.
[b]TEAEs considered by the investigator to be possibly or probably related to treatment; TEAEs with missing investigational drug relationship were classified as 'related'.
[c]By Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) preferred term occurring in ⩾5% of fampridine-SR-treated patients in either study.

>2.0. Two positive studies are normally required for regulatory approval.

No significant differences between treatments were observed in either study for the two co-primary end points, change from baseline of the Ashworth and SGI scores, averaged over the double-blind period. The SGI was used as a co-primary end point to determine the clinical meaningfulness of any changes in Ashworth score and to assess patient perceptions of potential negative drug effects that might have counterbalanced benefits. Thus, the SGI results can be considered to represent a mixed response, as there was neither a positive nor negative change in the mean score. The previous phase 2 study reported significantly improved SGI scores with fampridine-SR-treated relative to placebo but no significant difference in Ashworth score change, except for the subset of patients with more marked spasticity.[13]

Although the greater improvement in the Upper Extremity Spasm Frequency subscale with fampridine-SR compared with placebo in SCI-F302 was nominally significant ($P = 0.044$), there were no other significant between-treatment differences on the Penn Spasm Frequency Scale in either study. Self-report and clinical examination scales for spasticity assessment may represent different dimensions of the clinical problem of spasticity. In this regard, the Penn Spasm Frequency Score correlates significantly with clonus or perceived problematic spasticity that interferes with activities of daily living, and may not reflect the single-joint, velocity-dependent resistance to movement, as measured by the Ashworth scale.[18,19]

With respect to sexual function end points, no significant differences were observed between treatments for sexual function among women in either trial. Among men in SCI-F301, two IIEF domains were significantly improved at end point with fampridine-SR relative to placebo, erectile function ($P = 0.016$) and orgasmic function ($P = 0.032$), and another domain (intercourse satisfaction) trended toward significance ($P = 0.058$). Although these results are similar to the phase 2 trial,[13] sexual function was neither a primary focus of the current studies nor an inclusion criterion. Also, the nominal significance, achieved only in SCI-F301, was with end point analysis rather than the prespecified analysis of change from baseline averaged over double-blind treatment.

Although 25 mg twice daily is a higher dose than approved for the treatment of walking impairment in patients with multiple sclerosis,[20] the safety profile was generally consistent with previous studies evaluating fampridine-SR for SCI and multiple sclerosis.[6,13] There were no seizure-related TEAEs in either trial.

In summary, fampridine-SR 25 mg twice daily was generally well tolerated in patients with chronic incomplete SCI. However, no significant differences were observed between treatment groups for the primary end points. Although the efficacy reported in the phase 2 trial could not be confirmed, it is possible that functionally related end points may be necessary to observe effects. Interpretation of nominally significant changes on other end points should be made with caution, as these end points were not prospectively defined as part of the primary analysis of either study and represent subanalyses among multiple potential end points. It should also be noted that other than stable physical therapy regimens that had previously been initiated, these studies did not specifically include instructed activity such as physical therapy, range of motion or other physical interventions that have been endorsed as adjunctive to pharmacologic management of spasticity; insufficient data were available for analyzing the subset of patients undergoing physical therapy. Nevertheless, the overall results of previous studies and those reported here suggest that further evaluation of fampridine-SR may be warranted in patients with SCI. These evaluations could potentially build on the observation from studies in multiple sclerosis patients that only a subset of treated individuals respond to treatment.[6]

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

Dr Cardenas has received consulting fees from Coloplast A/C and Pfizer. Drs Lammertse and Alexander declare no conflict of interest. Drs Ditunno, Graziani and Potter have received consulting fees from

Acorda Therapeutics, Inc. Dr McLain (formerly Jackson) has received consulting fees from Pfizer and honoraria from the American Physician Institute for Advance Professional Studies, LLC. Drs Cohen and Blight are employees of Acorda Therapeutics, Inc., and hold stock in the company.

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