The Journal of Clinical Pharmacology 54(1) 53–60

DOI: 10.1002/jcph.189

Pharmacokinetics of Dalfampridine Extended Release 7.5-mg Tablets in Healthy Subjects and Individuals With Mild and Moderate Renal Impairment: An Open-Label Study

Emil Samara, PhD[1], Peter Winkle, MD[2], Patricia Pardo, MD[3], Herbert R. Henney III, PharmD[4], Susan L. Way, PhD[4], Eppie Brown, RN, MA[4], Angela Lee[4], and Andrew R. Blight, PhD[4]

Abstract

Dalfampridine extended release tablets (D-ER; prolonged-release fampridine in Europe) are available to improve walking in patients with multiple sclerosis (MS). D-ER is mainly renally eliminated; the approved 10-mg twice daily dose is contraindicated in the United States in patients with moderate or severe renal impairment. This study evaluated single-dose and steady-state pharmacokinetics of a 7.5-mg dose of D-ER in healthy subjects (n = 13) and subjects with mild (n = 17) and moderate (n = 12) renal impairment. D-ER plasma concentrations were consistently higher in subjects with renal impairment relative to healthy individuals with a significant ($P < .0001$) inverse linear relationship between creatinine clearance and drug exposure. Steady-state AUC_{0-12} among healthy subjects, 167.0 ± 55.3 ng h/mL, increased 74% and 151% with mild and moderate renal impairment, respectively. The overall incidence of adverse events was 61.5%, 47.1%, and 33.3% in healthy subjects, and subjects with mild and moderate renal impairment, respectively, and for treatment-related adverse events the rates were 0%, 17.6%, and 8.3%, respectively. The most common adverse events were headache, dizziness, and arthralgia. The pharmacokinetics of D-ER 7.5-mg twice daily in subjects with mild renal impairment was comparable to 10-mg twice daily in patients with MS who had normal renal function. Exposure was significantly higher in moderate renal impairment.

Keywords

dalfampridine, pharmacokinetics, moderate renal impairment, severe renal impairment, multiple sclerosis

Targeted treatment of symptoms and disabilities associated with multiple sclerosis (MS) is an important component of patient management.[1–3] Although medications are available for treating many MS symptoms, only in 2010 was a pharmacologic therapy approved specifically for improving walking impairment, the most common visible MS symptom. This drug, dalfampridine extended release tablets (D-ER; known as prolonged-release fampridine in Europe; sustained or modified release fampridine elsewhere) 10 mg twice daily, is available in the United States to improve walking in patients with MS as demonstrated by an increase in walking speed.[4] In Europe, it is indicated for the improvement of walking in adult patients with MS with walking disability (Expanded Disability Status Scale 4.0–7.0).[5]

Approval of D-ER was based on results from 2 phase 3 clinical trials in which the proportion of patients qualifying as timed walk responders was significantly greater with D-ER relative to placebo, 35% versus 8% ($P < .0001$) and 42.9% versus 9.3% ($P < .0001$) in the two studies, respectively.[6,7] In these studies, timed walk responders were prospectively defined as patients who had a faster walking speed on the Timed 25-Foot Walk for at least three of four visits during the double-blind treatment period compared with their maximum speed for any of the five off-drug evaluations. This response was found to be clinically meaningful from the patients' perspective by reference to changes in the 12-Item Multiple Sclerosis Walking Scale[8] among timed walk responders compared with non-responders. Additionally, D-ER timed walk responders demonstrated a significantly greater average improvement in walking speed during treatment relative to

[1]PharmaPolaris International, Davis, CA, USA
[2]Anaheim Clinical Trials, Anaheim, CA, USA
[3]MRA Clinical Research, South Miami, FL, USA
[4]Acorda Therapeutics, Inc., Ardsley, NY, USA

Submitted for publication 15 May 2013; accepted 17 September 2013.

Corresponding Author:
Emil Samara, PhD, PharmaPolaris International, Inc., 44282N El Macero Drive, Davis, CA, USA
E-mail: ESamara@PharmaPolaris.com

placebo in both trials (25.2% vs. 4.7% and 24.7% vs. 7.7%).[6,7]

Dalfampridine is a potassium channel blocker. Although the mechanism of action of dalfampridine has not been fully elucidated, it is thought to convey its clinical effects by restoring axonal conduction via blockade of the potassium channels that become exposed during demyelination.[9] This restoration of conduction putatively results from the demonstrated ability of dalfampridine to improve impulse propagation across demyelinated axons and maintain axonal conduction across the demyelinated internodes.[10,11] Dalfampridine has a narrow therapeutic range and the incidence of adverse events, including seizures, is dose related.[12]

The human pharmacokinetics (PK) of D-ER have been characterized,[13–17] and elimination is primarily (96%) via the renal route as unchanged drug.[13] A single-dose PK study in subjects with renal impairment reported that exposure to D-ER was significantly higher in these individuals than in healthy controls, with the extent of exposure dependent on level of impairment.[16] The potential for excessive accumulation with repeated dosing in individuals with moderate or severe renal impairment resulted in a contraindication in the United States for D-ER use in those populations.[4]

The objective of this study was to characterize the PK of D-ER 7.5-mg tablets in healthy adults with no renal impairment and in individuals with chronic mild or moderate renal impairment. This study was conducted in response to a U.S. Food and Drug Administration-required postmarketing commitment to assess the PK profile of a 7.5-mg tablet in subjects with renal impairment.

Methods

Study Design

This study was a non-randomized, parallel-group, open-label design to evaluate single-dose and multidose PK of D-ER 7.5-mg tablets in healthy volunteers (Group 1), and in individuals with mild (Group 2) or moderate (Group 3) renal impairment without MS. The study design was approved by Institutional Review Boards at the respective study sites (Advanced Clinical Research Institute [Anaheim, CA] and MRA Clinical Research [South Miami, FL]) and was conducted in accordance with the principles of the Declaration of Helsinki; all subjects provided written informed consent prior to participation.

Subjects

Subjects eligible for inclusion were men and non-pregnant, non-lactating women between the ages of 18 and 75 years inclusive, with a body mass index (BMI) ranging between 19.0 and 35.0 kg/m^2. Women of childbearing potential who were sexually active were required to have a negative serum pregnancy test and to agree to use a medically accepted method of birth control through completion of the study. Subjects were assigned to 1 of the following 3 groups based upon calculated creatinine clearance (CrCl) using the Cockcroft–Gault formula: normal renal function (Group 1; CrCl > 80 mL/min), mild renal impairment (Group 2; CrCl 51–80 mL/min), or moderate renal impairment (Group 3; CrCl 30–50 mL/min). Subjects were excluded if they had used another investigational drug during the past 30 days; had a history of seizures or had received therapy for a seizure disorder at any time in the past; had a known allergy to pyridine-containing substances; or had donated ≥1 pint of blood within 60 days prior to study drug administration or donated plasma within 7 days prior to study drug administration. Other exclusion criteria included a history of drug or alcohol abuse in the past 2 years, a positive test for drugs of abuse at screening, and the presence of any unstable cardiovascular, enterohepatic, respiratory, or immunologic disorder or disease that might substantially affect the PK of D-ER. Concomitant medications were allowed provided the doses had been stable for at least 30 days prior to screening; initiation of new medications was not permitted during the study.

Protocol

All subjects received a 7.5-mg D-ER tablet orally with water once on Day 1, twice daily on Days 2 through 5, and a final dose on Day 6. Within 2 weeks following screening, subjects were admitted to the study site the night prior to the first dalfampridine dose for an approximately 36-hour confinement period during which they observed an overnight fast of at least 6 hours. The following morning (Day 1), subjects were administered a single D-ER 7.5-mg tablet with water, and were provided a standardized meal 4 and 9 hours after dosing. Day 1 blood samples were at baseline (15 minutes prior to dosing) and at 1, 2, 3, 4, 5, 6, 8, 12, and 16 hours post-dose, with a 24-hour post-dose sample obtained on Day 2. After the 24-hour blood sample on Day 2, a second 7.5-mg dose of D-ER was administered and subjects were discharged after completion of safety evaluations. At discharge, subjects received a 3-day supply of D-ER 7.5 mg and were instructed to take one tablet every 12 hours. Subjects were contacted by phone on Days 3 and 4 to remind them to take the drug and to inquire about their general condition.

Subjects returned to the study site on the evening of Day 5 for a second confinement period during which they were administered a 7.5-mg dose of D-ER. The final 7.5-mg dose was approximately 12 hours later, on the morning of Day 6, approximately 1 hour after a standard clinic breakfast. On Day 6, blood samples were obtained 15 minutes prior to dosing and at the same post-dose time points as that for Day 1, with further 24- and 36-hour post-dose samples obtained on Day 7. Subjects were discharged on the evening of Day 7 after the final blood

samples were obtained and after completion of safety evaluations.

Approximately 10 mL of blood was collected at each time point using heparinized Vacutainer tubes (BD Diagnostics, Franklin Lakes, NJ) and centrifuged at low speed (1,500*g*; approximately 3,000 rpm) for 10 minutes at 4°C. Approximately 3 mL of plasma was obtained, which was transferred into a labeled tube and stored at −20°C until analysis was performed (Covance Laboratories, Inc., Madison, WI).

Plasma samples were analyzed using a proprietary validated liquid chromatography with tandem mass spectrometric (LC–MS–MS) detection in positive electrospray mode (Covance Laboratories, Inc.). As described in a previous study,[17] assay performance was monitored by spiking blank interference-free human plasma with dalfampridine and internal standards to generate standard-curve and quality control (QC) samples. For precision, the intraassay and interassay results demonstrated a relative standard deviation of ≤15.0% (≤20.0% at the lower limit of quantification [LLOQ]) for QC samples. Samples were determined to be interference free if the relevant regions of LC–MS–MS assay demonstrated <20.0% of the mean utilized LLOQ or <5.0% of the internal standard response of the control zero sample. The accuracy of the method, determined by comparing the means of the measured concentrations of the intraassay and interassay QC samples with their theoretical concentrations, was demonstrated to be within the range of 85.0–115.0% (80.0–120.0% at the LLOQ); the LLOQ was 1.0 ng/mL, and linearity was demonstrable to 1,000 ng/mL (the upper limit of quantitation) using a sample volume of 0.05 mL.

PK and Statistical Analysis

Plasma PK parameters were evaluated for both the first (single dose) and last (steady-state) doses from the individual plasma concentrations using non-compartmental methods (WinNonlin Version 5.0; Pharsight Corporation, Mountain View, CA). Plasma concentrations below the LLOQ were set to "0" for the PK analyses and summary statistics.

The plasma PK parameters calculated were the observed maximum plasma concentration (C_{max}), the time from dosing to C_{max} (T_{max}), the observed trough concentration at steady-state (C_{min}), and the area under the plasma concentration versus time curve (AUC) until the last measurable concentration ($AUC_{0–last}$) and over one dosing interval of 12 hours ($AUC_{0–12}$), which were calculated using the linear trapezoidal rule. The $AUC_{0–last}$ was extrapolated to infinity ($AUC_{0–\infty}$) for single dosing by adding the quotient of k_{el} and the last measurable concentration; the apparent terminal half-life ($t_{1/2}$) was calculated from the slope of the terminal phase; and apparent clearance (CL/F; total body clearance uncorrected for oral bioavailability) was calculated as the quotient of $AUC_{0–\infty}$ (after single dose) or $AUC_{0–12}$ (at steady-state) and dose.

Subjects who took at least 1 dose of the study drug and had any post-dosing plasma concentration data were included in descriptive statistics, which were tabulated for the PK parameters among the three groups. Descriptive statistics included the mean value with standard deviation (SD) for all PK variables except T_{max}, which is presented as the median statistic since T_{max} times were discrete and were summarized by frequency at each sampling time point. Analysis of variance (ANOVA) models were used for the natural log-transformed PK parameters ($AUC_{0–last}$, $AUC_{0–inf}$, and C_{max}) for pairwise statistical comparison of the ratios of arithmetic least squares means; an alpha = 0.05 using a one-sided test was considered to indicate statistical significance. Residual analysis was used to confirm that model assumptions were reasonable, and the ANOVA analyses were also repeated using weight-adjusted PK parameters.

Safety Evaluation

Safety assessment of all subjects receiving at least 1 dose of study medication was based on incidence and severity of treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory tests, and physical examinations. A follow-up safety evaluation was conducted by phone 3 days after final clinic discharge. Laboratory tests performed before dosing included blood hematology and full clinical chemistry panels and urinalysis. Pregnancy testing for women of child-bearing potential was performed at screening and Day 7.

Results

Demographics

Of 106 subjects who were screened for eligibility, 42 were enrolled in the study and assigned to 1 of 3 groups based on their degree of renal impairment; healthy volunteers (Group 1; n = 13), subjects with mild renal impairment (Group 2; n = 17), and subjects with moderate renal impairment (Group 3; n = 12). All subjects completed the study except for 1 volunteer in Group 1 who was lost to follow-up following Day 2.

As shown in Table 1, subjects were evenly matched across groups for the demographic characteristics of race and BMI. However, there was imbalance with respect to gender and age, with the healthy volunteer group having a higher proportion of men and a lower mean age than the 2 groups with renal impairment (Table 1).

PK Profile

The peak and extent of exposure to D-ER 7.5 mg in the three cohorts are shown graphically in Figure 1A for single doses and 1B for steady-state.

Table 1. Demographic Characteristics of the Study Cohorts

Variable	Group 1 Healthy Subjects (n = 13)	Group 2 Mild Renal Impairment (n = 17)	Group 3 Moderate Renal Impairment (n = 12)
Sex, n (%)			
Male	10 (76.9)	10 (58.8)	8 (66.7)
Female	3 (23.1)	7 (41.2)	4 (33.3)
Age, years, mean ± SD	41 ± 15	63 ± 7	67 ± 8
Race, n (%)			
White	11 (85)	11 (65)	8 (67)
Black or African American	1 (8)	2 (12)	2 (17)
Asian	0	4 (23.5)	2 (17)
Other	1 (8)	0	0
Body weight, kg, mean ± SD	83 ± 16	76 ± 10	80 ± 19
BMI, kg/m^2, mean ± SD	28 ± 5	28 ± 3	28 ± 3
CrCl, L/min, mean ± SD	130 ± 35	63 ± 10	40 ± 6

BMI, body mass index; CrCl, creatinine clearance; SD, standard deviation.

A single dose of D-ER 7.5-mg tablets in individuals with normal renal function resulted in a mean C_{max} of 14.9 ± 4.3 ng/mL that was achieved at a median T_{max} of 3 hours (Table 2), mean apparent clearance (CL/F) was 51.7 ± 23.0 L/h, and the mean $AUC_{0-\infty}$ was 169.4 ± 67.8 ng h/mL. The CL/F was reduced by 43% and 63%, respectively, in subjects with mild and moderate renal impairment, resulting in higher drug exposure, measured by C_{max} and AUC, relative to Group 1 controls (Table 2). The $AUC_{0-\infty}$ and C_{max} values were 281.1 ± 82.0 ng h/mL and 19.3 ± 5.3 ng/mL for mild renal impairment and 411.1 ± 94.3 ng h/mL and 23.8 ± 4.7 ng/mL for moderate renal impairment, respectively. As renal impairment increased, the single-dose elimination rate constant (K_{el}) decreased by 21% with mild impairment and 37% with moderate impairment. The $t_{1/2}$ increased as renal impairment increased averaging 5.3, 6.6, and 9.0 hours, respectively, in healthy subjects, subjects with mild renal impairment, and subjects with moderate renal impairment.

Similar to the single dose PK, summary PK statistics at steady-state revealed greater drug exposure with increasing renal impairment relative to the individuals with normal renal function (Table 3). The AUC_{0-12} was 167.0 ± 55.3 ng h/mL among Group 1 subjects, 290.8 ± 101.8 ng h/mL for mild renal impairment (Group 2), and 419.5 ± 58.4 ng h/mL for moderate renal impairment (Group 3). Additionally, the steady-state C_{max} was 67% higher for subjects with mild impairment and 121% higher for those with moderate impairment compared to subjects with normal renal function. The higher exposure observed among those with renal impairment resulted from slower apparent renal clearance; as CL/F decreased with renal impairment, there was a corresponding increase in steady state $t_{1/2}$, and reductions in K_{el}, by 10% and 32% with mild and moderate impairment, respectively. The average C_{min} values also increased relative to healthy subjects by 87% in mild impairment and 223% in those with moderate impairment.

Statistical Analyses

All pairwise single-dose comparisons demonstrated significant differences among the cohorts (Table 4). The largest ratios indicated the relative differences in drug exposure observed for the comparison of moderate renal impairment with healthy subjects, which were 1.63, 2.56, and 0.39, respectively, for C_{max}, $AUC_{0-\infty}$, and CL/F.

All pairwise comparisons for steady-state variables were also significant (Table 4). Similar to single dosing, the largest ratios observed were for the comparison between moderate renal impairment and healthy subjects, which were 2.27, 2.63, and 0.38 for C_{max}, AUC_{0-12}, and CL/F, respectively. In contrast, comparisons of moderate and mild renal impairment revealed the smallest ratios. Repeating the ANOVA analyses, while including body weight as a covariate, did not affect the outcome.

Regression analyses to characterize the relationship between renal function and PK parameter estimates at steady-state suggested a linear relationship between CrCl and C_{max} (Figure S1A), AUC_{0-12} (Figure S1C), and CL/F (Figure S1E). Natural log-transformations of the data improved the model, confirming linearity with R^2 values of 0.4273 for C_{max} ($P < .0001$; Figure S1B), 0.3796 for AUC_{0-12} ($P < .0001$; Figure S1D), and 0.7999 for CL/F ($P < .0001$; Figure S1F).

Tolerability

The incidence of TEAEs was 61.5%, 47.1%, and 33.3% in Groups 1, 2, and 3, respectively (Table 5). There were no serious TEAEs and none of the TEAEs led to discontinuation of the study. TEAEs were assessed by the investigator to be treatment related only in individuals with renal impairment (Table 5). These events included one subject with frequent bowel movements, one subject with both

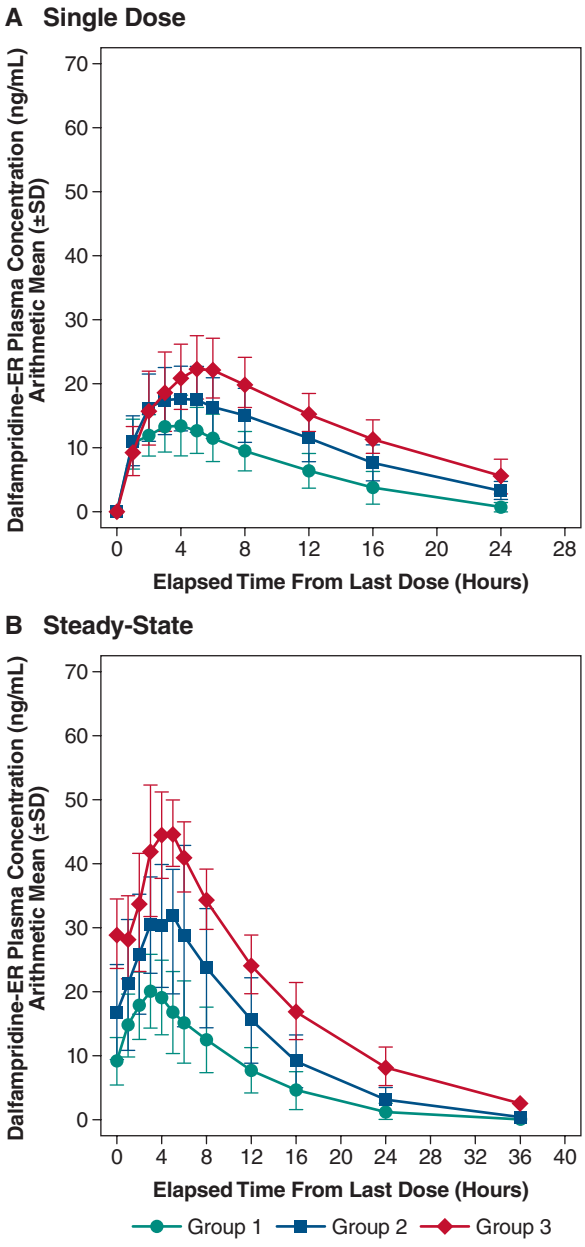

Figure 1. Mean plasma concentrations versus time for dalfampridine 7.5 mg by renal function group: Group 1 = healthy subjects with no renal impairment; Group 2 = subjects with mild renal impairment; and Group 3 = subjects with moderate renal impairment. (A) After single dose administration. (B) Steady-state concentrations. Dalfampridine-ER, dalfampridine extended release; SD, standard deviation.

myalgia and increased creatinine phosphokinase, and one subject with headache, all in Group 2, and one subject with diarrhea in Group 3.

The most common TEAEs were headache, dizziness, and arthralgia (Table 5), and there did not appear to be any clear pattern to their occurrence among the three study cohorts. There were no clinically important trends in laboratory variables, and no clinically significant electrocardiogram abnormalities were observed.

Discussion

A previous single-dose study demonstrated a statistically significant and strong inverse linear relationship between CrCl and exposure to dalfampridine, and that repeated dosing of D-ER resulted in increased accumulation of drug in individuals with renal impairment.[16] Because steady-state PK data have not been studied previously in subjects with renal impairment, the current study was undertaken to characterize the steady-state PK of dalfampridine following a D-ER 7.5-mg dose twice daily in healthy subjects and those with mild and moderate renal impairment. A previous study of the effect of food on D-ER absorption described a modest increase in C_{max} from 23.8 ng/mL in the fasted state to 28.9 ng/mL when given with food.[17] However, the increase was not accompanied by any significant change in systemic exposure, and therefore, the current study evaluated steady-state PK after a breakfast meal.

As is common in this type of study, the mean age of the healthy volunteer cohort (42 years) was younger than the mild and moderate renal impairment groups (63 and 67 years, respectively). Interestingly, the mean BMI was similar across the three groups. Although the gender and race distribution was similar across the groups, it is different than the MS population, where 2–3 times as many women are affected as men.[18] Nevertheless, this difference is unlikely to affect the study outcome. Indeed, the results appear to be consistent with PK data reported from studies of D-ER that were performed in people with MS.[6,7,14,15]

Following a single D-ER 7.5-mg dose, the C_{max} and $AUC_{0-\infty}$ for subjects with mild renal impairment, 19.3 ng/mL and 281.1 ng h/mL, respectively, were consistent with those previously reported in subjects with normal renal function for a 10-mg dose, 21.6 ng/mL for C_{max} and 284.8 ng h/mL for $AUC_{0-\infty}$.[16] The 66% and 143% increase in exposure ($AUC_{0-\infty}$) for subjects with mild and moderate renal impairment, respectively, compared with healthy subjects was similar to the 76% and 108% increases in $AUC_{0-\infty}$ observed in subjects with mild and moderate renal impairment, respectively, following a 10-mg dose.[16]

At steady-state, subjects with mild and moderate renal impairment had increases in C_{max} of 67% and 121%, respectively, and increases in AUC_{0-12} were 74% and 151% for mild and moderate renal impairment, respectively, compared with healthy subjects. This increased exposure, resulting from an apparent total body clearance (CL/F) that was just over one-half (55.8%) and one-third (36.0%), respectively, of that among healthy subjects. Although C_{min} in healthy subjects was 9.0 ng/mL, it was 16.8 and 29.1 ng/mL in those with mild and moderate impairment, respectively.[19] Despite the decrease in apparent clearance in subjects with mild renal impairment,

Table 2. Summary Statistics of Single Dose Non-Compartmental PK for D-ER 7.5-mg Dose

Parameter	Group 1 Healthy Subjects (n = 13)	Group 2 Mild Renal Impairment (n = 17)	Group 3 Moderate Renal Impairment (n = 12)
C_{max}, ng/mL	14.9 ± 4.3	19.3 ± 5.3	23.8 ± 4.7
T_{max}, hour, median	3.0	3.0	5.0
$AUC_{0-\infty}$, ng h/mL	169.4 ± 67.8	281.1 ± 82.0	411.1 ± 94.3
K_{el}, 1/h	0.140 ± 0.037	0.111 ± 0.027	0.088 ± 0.033
$t_{1/2}$, hour	5.3 ± 1.4	6.6 ± 1.5	9.0 ± 3.5
CL/F, L/h	51.7 ± 23.0	29.4 ± 10.3	19.1 ± 3.9

$AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; D-ER, dalfampridine extended release; K_{el}, elimination rate constant; PK, pharmacokinetics; T_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.
Values are arithmetic means ± SDs, except for T_{max}, for which the median is presented.

the mean steady-state plasma concentrations did not exceed what has been reported in clinical trials of D-ER.[6,7]

The steady-state data suggest, in subjects with mild renal impairment, that the average dalfampridine C_{max} produced by a D-ER 7.5-mg twice daily dose—35.5 ng/mL—would be similar to that produced by a 10-mg twice daily dose in persons with MS with normal renal function. In earlier studies of D-ER, a C_{max} of 28.9 ng/mL dalfampridine was reported under fed conditions after a single 10-mg dose,[17] and steady-state C_{max} of 25.3 ng/mL was reported for 10 mg twice daily, under fasted conditions in healthy subjects.[20] Additionally, in clinical trials, mean plasma concentrations of dalfampridine at each visit during double-blind treatment were 27.6–29.2 ng/mL[6] and 28.5–30.2 ng/mL.[7] Although this study was conducted in volunteers without MS, the data nevertheless suggest that a 7.5-mg tablet may have benefit for people with MS who also have mild renal impairment.

Comparison of the single-dose and steady-state PK parameters demonstrates a clear linear relationship between dose and renal function. Comparing both single dose and steady state C_{max} accumulation ratios showed a stepwise and statistically significant increase for the two renal impairment groups compared with normal renal function. However, the large inter-subject variability is also evident in these data (Table 4).

In this study, D-ER 7.5 mg was well tolerated in healthy subjects as well as in those with mild and moderate renal impairment. Headache and dizziness were the most frequently reported adverse events, and all reported adverse events had previously been detected and reported during the D-ER clinical development program.[12] No clinically relevant trends were observed in any of the evaluated clinical or laboratory safety parameters, and no safety signals emerged among the subjects with renal impairment.

The results of this study should be interpreted within the context of its limitations, which include the fact that it was conducted in volunteers who did not have MS. Furthermore, since the healthy volunteers were significantly younger than those with mild and moderate renal impairment, this age difference could impact the PK beyond the obvious differences in renal impairment. Given the more rapid renal excretion seen in younger individuals, the study results likely overestimate the group differences in drug exposure that would be seen between

Table 3. Summary Statistics of Non-Compartmental PK at Steady-State for D-ER 7.5-mg Dose

Parameter	Group 1 Healthy Subjects (n = 13)	Group 2 Mild Renal Impairment (n = 17)	Group 3 Moderate Renal Impairment (n = 12)
C_{max}, ng/mL	21.3 ± 5.5	35.5 ± 12.3	47.0 ± 6.0
T_{max}, hour, median	3.0	3.0	4.0
C_{min}, ng/mL	9.0 ± 3.7	16.8 ± 7.3	29.1 ± 5.4
AUC_{0-12}, ng h/mL	167. 0 ± 55.3	290.8 ± 101.8	419.5 ± 58.4
K_{el}, 1/h	0.146 ± 0.040	0.131 ± 0.027	0.100 ± 0.023
$t_{1/2}$, hour	5.0 ± 1.1	5.5 ± 1.1	7.2 ± 1.7
CL/F, L/h	50.9 ± 22.1	28.4 ± 8.8	18.3 ± 3.0

AUC_{0-12}, area under the plasma concentration–time curve over 1 dosing interval of 12 hours; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; C_{min}, trough plasma concentration; D-ER, dalfampridine extended release; K_{el}, elimination rate constant; PK, pharmacokinetics; T_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.
Values are arithmetic means ± SDs except for T_{max}, for which the median is presented.

Table 4. Pairwise Statistical Comparison of Single-Dose and Steady-State PK Ratios of D-ER 7.5-mg Dose

	Single-Dose Ratios (90% CI) of LS Means			Steady-State Ratios (90% CI) of Geometric LS Means		
	Mild Renal Impairment/ Healthy; *P*-Value[a]	Moderate Renal Impairment/Healthy; *P*-Value[a]	Moderate Renal Impairment/ Mild Renal Impairment; *P*-Value[a]	Mild Renal Impairment/ Healthy; *P*-Value[a]	Moderate Renal Impairment/ Healthy; *P*-Value[a]	Moderate Renal Impairment/ Mild Renal Impairment; *P*-Value[a]
C_{max}	1.30 (1.11–1.52); .0078	1.63 (1.37–1.94); <.0001	1.25 (1.07–1.47); .0243	1.65 (1.40–1.94); <.0001	2.27 (1.99–2.70); <.0001	1.38 (1.17–1.62); .0021
C_{min}	—	—	—	1.87 (1.67–2.39); .0001	3.46 (2.66–4.50); <.0001	1.85 (1.45–2.36); .0001
AUC_{0-last}	1.72 (1.41–2.10); <.0001	2.34 (1.89–2.90); <.0001	1.36 (1.11–1.66); .0148	—	—	—
$AUC_{0-\infty}$	1.71 (1.40–2.10); <.0001	2.56 (2.05–3.19); <.0001	1.50 (1.22–1.84); .0023	—	—	—
AUC_{0-12}	—	—	—	1.75 (1.45–2.12); <.0001	2.63 (2.14–3.23); <.0001	1.50 (1.24–1.82); .0009
CL/F	0.58 (0.48–0.72); .0001	0.39 (0.31–0.49); <.0001	0.67 (0.54–0.82); .0023	0.57 (0.47–0.72); <.0001	0.38 (0.31–0.47); <.0001	0.67 (0.55–0.81); .0009

$AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration versus time curve over the evaluated time interval; AUC_{0-12}, area under the plasma concentration–time curve over 1 dosing interval of 12 hours; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; C_{min}, trough plasma concentration; D-ER, dalfampridine extended release; LS, least squares; PK, pharmacokinetics.

[a]*P*-values are reported at the nominal level without any adjustment.

Table 5. Treatment-Emergent Adverse Events

	Incidence, n (%)		
	Group 1 Healthy Subjects (n = 13)	Group 2 Mild Impairment (n = 17)	Group 3 Moderate Impairment (n = 12)
Any TEAE	8 (61.5)	8 (47.1)	4 (33.3)
Serious TEAEs	0	0	0
TEAEs related to study drug	0	3 (17.6)	1 (8.3)
Severe TEAEs	0	0	0
TEAEs leading to discontinuation	0	0	0
Most common TEAEs[a]			
Headache	2 (15.4)	3 (17.6)	0
Dizziness	2 (15.4)	1 (5.9)	1 (8.3)
Arthralgia	0	0	2 (16.7)

TEAEs, treatment-emergent adverse events.

[a]By MedDRA Preferred Term occurring in ≥2 subjects in any group.

older MS patients with and without renal impairment. However, the significant accumulation of dalfampridine in patients with moderate renal impairment confirms the current contraindication to use in these patients.

In conclusion, the data from this study revealed that the PK profile for D-ER 7.5 mg, which was administered twice daily, in subjects with renal impairment was consistent with expectations based on an earlier study.[16] In subjects with mild renal impairment, the PK of D-ER 7.5 mg was generally comparable with that of 10 mg twice daily in persons with MS with normal renal function. While the PK results suggest that an additional safety margin could be realized by using a 7.5 mg dose in patients with mild impairment, the group difference in exposure is small relative to the intra-patient variability within groups, and current experience with D-ER does not substantiate the need for a lower strength tablet of dalfampridine for patients with mild renal impairment.

Declaration of Conflicting Interests

Dr. Samara is a paid consultant for Acorda Therapeutics, Inc. and is an employee of PharmaPolaris International, Inc., who was contracted by Acorda Therapeutics as a clinical pharmacology advisor.

Funding

Drs. Winkle and Pardo have received research/grant support from Acorda Therapeutics, Inc., Ms. Brown, Ms. Lee, Dr. Henney, and Dr. Blight are employees and stockholders of Acorda Therapeutics, Inc. This study was sponsored by Acorda Therapeutics, Inc. Editorial assistance was provided by The Curry Rockefeller Group, LLC, Tarrytown, NY, and was funded by Acorda Therapeutics, Inc.

References

1. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. *Lancet Neurol.* 2010;9(12):1182–1199.
2. de Sa JC, Airas L, Bartholome E, et al. Symptomatic therapy in multiple sclerosis: a review for a multimodal approach in clinical practice. *Ther Adv Neurol Disord.* 2011;4(3):139–168.
3. Samkoff LM, Goodman AD. Symptomatic management in multiple sclerosis. *Neurol Clin.* 2011;29(2):449–463.
4. *Ampyra (Dalfampridine) Extended Release Tablets [Prescribing Information]*. Ardsley, NY: Acorda Therapeutics, Inc; 2013.
5. European Medicines Agency Committee for Medicinal Products for Human Use. Summary of opinion (initial authorisation) for Fampyra (fampridine). http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002097/WC500106531.pdf Accessed May 3, 2013.
6. Goodman AD, Brown TR, Krupp L, et al. Fampridine MS-F203 investigators. Sustained release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet.* 2009; 373(9665):732–738.
7. Goodman AD, Brown TR, Edwards KR, et al. MS-F204 investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. *Ann Neurol.* 2010;68(4):494–502.
8. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology.* 2003;60(1):31–36.
9. Dunn J, Blight A. Dalfampridine: a brief review of its mechanism of action and efficacy as a treatment to improve walking in patients with multiple sclerosis. *Curr Med Res Opin.* 2011;27(7):1415–1423.
10. Targ EF, Kocsis JD. 4-Aminopyridine leads to restoration of conduction in demyelinated rat sciatic nerve. *Brain Res.* 1985;328(2):358–361.
11. Shi R, Blight AR. Differential effects of low and high concentrations of 4-aminopyridine on axonal conduction in normal and injured spinal cord. *Neuroscience.* 1997;77(2):553–562.
12. Cornblath D, Bienen EJ, Blight A. The safety profile of dalfampridine extended release in multiple sclerosis clinical trials. *Clin Ther.* 2012;34(5):1056–1069.
13. Blight AR, Henney HR III. Pharmacokinetics of 14C-radioactivity after oral intake of a single dose of 14C-labeled fampridine (4-aminopyridine) in healthy volunteers. *Clin Ther.* 2009;31(2):328–335.
14. Vollmer T, Henney HR III. Pharmacokinetics and tolerability of single escalating doses of fampridine sustained-release tablets in patients with multiple sclerosis: a phase I-II, open-label trial. *Clin Ther.* 2009;31(10):2206–2214.
15. Vollmer T, Blight AR, Henney HR III. Steady-state pharmacokinetics and tolerability of orally administered fampridine sustained release 10-mg tablets in patients with multiple sclerosis: a 2-week, open-label, follow-up study. *Clin Ther.* 2009;31(10):2215–2223.
16. Smith W, Swan S, Marbury T, Henney H III. Single-dose pharmacokinetics of sustained-release fampridine (Fampridine-SR) in healthy volunteers and adults with renal impairment. *J Clin Pharmacol.* 2010;50(2):151–159.
17. Henney HR III, Faust B, Blight AR. Effect of food on the single-dose pharmacokinetics and tolerability of dalfampridine extended-release tablets in healthy volunteers. *Am J Health Syst Pharm.* 2011;68(22): 2148–2154.
18. National Multiple Sclerosis Society. Who gets MS? http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx Accessed May 3, 2013.
19. Schapiro R, Brown T, Goodman A, et al. MS-F202, MS-F203, MS-F204 Study Groups. Doses of dalfampridine extended release tablets greater than 10 mg twice daily are associated with increased adverse events but not increased efficacy [poster P03.236]. *Neurology.* 2011;76(suppl 4):A245.
20. March B, Cardi T. Assessment of the cardiac safety of fampridine-SR sustained-release tablets in a thorough QT/QTc evaluation at therapeutic and supratherapeutic doses in healthy individuals. *Expert Opin Invest Drugs.* 2009;18(12):1807–1815.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.