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

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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<sub>0-12</sub> 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. 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. 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). 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. 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 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
placebo in both trials (25.2% vs. 4.7% and 24.7% vs. 7.7%).

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. 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. Dalfampridine has a narrow therapeutic range and the incidence of adverse events, including seizures, is dose related.

The human pharmacokinetics (PK) of D-ER have been characterized and elimination is primarily (96%) via the renal route as unchanged drug. 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. 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.

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/m². 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 (1,500g; 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, 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\text{max}), the time from dosing to C\text{max} (T\text{max}), the observed trough concentration at steady-state (C\text{min}), and the area under the plasma concentration versus time curve (AUC) until the last measurable concentration (AUC\text{0–last}) and over one dosing interval of 12 hours (AUC\text{0–12}), which were calculated using the linear trapezoidal rule. The AUC\text{0–last} was extrapolated to infinity (AUC\text{0–∞}) for single dosing by adding the quotient of k\text{d} and the last measurable concentration; the apparent terminal half-life (t\text{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\text{0–∞} (after single dose) or AUC\text{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\text{max}, which is presented as the median statistic since T\text{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\text{0–last}, AUC\text{0–inf}, and C\text{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.
A single dose of D-ER 7.5-mg tablets in individuals with normal renal function resulted in a mean $C_{\text{max}}$ of 14.9 ± 4.3 ng/mL that was achieved at a median $T_{\text{max}}$ of 3 hours (Table 2), mean apparent clearance ($\text{CL/F}$) was 51.7 ± 23.0 L/h, and the mean AUC$_{0-\infty}$ was 169.4 ± 67.8 ng h/mL. The $\text{CL/F}$ was reduced by 43% and 63%, respectively, in subjects with mild and moderate renal impairment, resulting in higher drug exposure, measured by $C_{\text{max}}$ and AUC, relative to Group 1 controls (Table 2). The AUC$_{0-\infty}$ and $C_{\text{max}}$ 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 ($K_{\text{el}}$) 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 $C_{\text{max}}$ 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 $\text{CL/F}$ decreased with renal impairment, there was a corresponding increase in steady state $t_{1/2}$, and reductions in $K_{\text{el}}$, by 10% and 32% with mild and moderate impairment, respectively. The average $C_{\text{min}}$ 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 $C_{\text{max}}$, AUC$_{0-\infty}$, and $\text{CL/F}$. 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 $C_{\text{max}}$, AUC$_{0-\infty}$, and $\text{CL/F}$, 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 $C_{\text{max}}$ (Figure S1A), AUC$_{0-12}$ (Figure S1C), and $\text{CL/F}$ (Figure S1E). Natural log-transformations of the data improved the model, confirming linearity with $R^2$ values of 0.4273 for $C_{\text{max}}$ ($P < .0001$; Figure S1B), 0.3796 for AUC$_{0-12}$ ($P < .0001$; Figure S1D), and 0.7999 for $\text{CL/F}$ ($P < .0001$; 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

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**Table 1. Demographic Characteristics of the Study Cohorts**

| Variable                        | Group 1 Healthy Subjects | Group 2 Mild Renal Impairment | Group 3 Moderate Renal Impairment |
|---------------------------------|--------------------------|-------------------------------|----------------------------------|
| 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/m², 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.
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. 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 $C_{\text{max}}$ from 23.8 ng/mL in the fasted state to 28.9 ng/mL when given with food. 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. 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.

Following a single D-ER 7.5-mg dose, the $C_{\text{max}}$ 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 $C_{\text{max}}$ and 284.8 ng h/mL for AUC$_{0-\infty}$. 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.

At steady-state, subjects with mild and moderate renal impairment had increases in $C_{\text{max}}$ 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 $C_{\text{min}}$ 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. Despite the decrease in apparent clearance in subjects with mild renal impairment,
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 Cmax 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 Cmax of 28.9 ng/mL dalfampridine was reported under fed conditions after a single 10-mg dose,17 and steady-state Cmax 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/mL6 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 Cmax 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

| Parameter | Group 1 Healthy Subjects | Group 2 Mild Renal Impairment | Group 3 Moderate Renal Impairment |
|-----------|--------------------------|-------------------------------|----------------------------------|
|           | (n = 13)                 | (n = 17)                      | (n = 12)                         |
| Cmax, ng/mL| 14.9 ± 4.3               | 19.3 ± 5.3                    | 23.8 ± 4.7                      |
| Tmax, hour, median | 3.0                     | 3.0                           | 5.0                             |
| AUC0–∞, ng h/mL | 169.4 ± 67.8            | 281.1 ± 82.0                  | 411.1 ± 94.3                   |
| Kel, l/h    | 0.140 ± 0.03 | 0.111 ± 0.027               | 0.088 ± 0.033                  |
| t1/2, 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                     |

AUC0–∞, area under the plasma concentration–time curve extrapolated to infinity; CL/F, apparent total body clearance; Cmax, maximum plasma concentration; Kel, elimination rate constant; PK, pharmacokinetics; Tmax, time to Cmax; t1/2, terminal half-life.

Values are arithmetic means ± SDs, except for Tmax, for which the median is presented.

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| Parameter | Group 1 Healthy Subjects | Group 2 Mild Renal Impairment | Group 3 Moderate Renal Impairment |
|-----------|--------------------------|-------------------------------|----------------------------------|
|           | (n = 13)                 | (n = 17)                      | (n = 12)                         |
| Cmax, ng/mL| 21.3 ± 5.5               | 35.5 ± 12.3                  | 47.0 ± 6.0                      |
| Tmax, hour, median | 3.0                     | 3.0                           | 4.0                             |
| Cmin, ng/mL| 9.0 ± 3.7                | 16.8 ± 7.3                   | 29.1 ± 5.4                      |
| AUC0–12, ng h/mL | 167.0 ± 55.3          | 290.8 ± 101.8                | 419.5 ± 58.4                   |
| Kel, l/h    | 0.146 ± 0.040            | 0.131 ± 0.027               | 0.100 ± 0.023                  |
| t1/2, 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                     |

AUC0–12, area under the plasma concentration–time curve over 1 dosing interval of 12 hours; CL/F, apparent total body clearance; Cmax, maximum plasma concentration; Cmin, trough plasma concentration; D-ER, dalfampridine extended release; Kel, elimination rate constant; PK, pharmacokinetics; Tmax, time to Cmax; t1/2, terminal half-life.

Values are arithmetic means ± SDs, except for Tmax, for which the median is presented.
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. In subjects with mild renal 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.

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Supporting Information

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