Original Research

A Phase I, Randomized, Crossover, Open-label Study of the Pharmacokinetics of Solriamfetol (JZP-110) in Healthy Adult Subjects With and Without Food

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ABSTRACT

Purpose: Solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor with robust wake-promoting effects, is currently being evaluated for the reduction of sleepiness and improvement of wakefulness in patients with narcolepsy and obstructive sleep apnea. The purpose of this study was to evaluate the effect of food on the pharmacokinetic (PK) parameters and bioavailability of solriamfetol at the highest intended therapeutic dose in healthy adults and to characterize its renal excretion under fasting conditions.

Methods: In this open-label, randomized, crossover study, healthy adult subjects received a single 300-mg dose of solriamfetol in a fasted condition (10 h) and in a fed condition (30 min after the start of a standardized high-fat, high-calorie breakfast), with at least a 7-day washout period between doses. Blood samples for PK analyses were collected during both conditions at prespecified time points. Urine samples were collected up to 48 h postdose in the fasted condition. Samples were analyzed for solriamfetol (plasma and urine) and *N*-acetyl solriamfetol (urine) by using validated LC-MS/MS bioanalytical methods. The effect of food on solriamfetol relative bioavailability was examined by comparing the 90% confidence intervals (CIs) of the fed/fasted ratios of natural log-transformed PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ with the prespecified range of 80%–125%. Safety and tolerability were also assessed.

Findings: A total of 32 subjects were enrolled (50% female; 53.1% black, 46.9% white; mean age, 35.6 years), and 31 were included in the PK analyses. Solriamfetol was rapidly absorbed in both conditions. The 90% CIs for the fed/fasted geometric mean ratios were 89.2–98.8 for C_{max} (ratio of 93.9%) and 93.8–101.5 for $AUC_{0-\infty}$ (ratio of 97.6%), indicating the absence of a food effect. In the fasted condition, 89.8% of solriamfetol was recovered in urine as unchanged drug over 48 h; 1.1% was excreted as a minor metabolite, *N*-acetyl solriamfetol. A total of 55 adverse events (AEs), all mild, were reported by 18 subjects (56.3%). The frequency and type of AEs were similar in the 2 conditions; the most common AEs (insomnia, headache, hypervigilance, decreased appetite, and nausea) were all mild in severity and resolved without treatment.

Implications: Solriamfetol relative bioavailability was bioequivalent in the fed and fasted conditions, showing that solriamfetol can be taken without regard to meals; furthermore, tolerability was similar in both conditions. Renal excretion of unchanged drug is the primary route of elimination. (*Clin Ther.* 2019;41:196–204)

Keywords: bioequivalence, food effects, JZP-110, pharmacokinetics, renal excretion, solriamfetol.

INTRODUCTION

Narcolepsy is a chronic neurologic disease with an onset that generally occurs during childhood or

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adolescence.[1,2] Obstructive sleep apnea (OSA) is a sleep-related breathing disorder that is associated with predisposing factors, including male sex, older age, and obesity.[3] Excessive daytime sleepiness is a major presenting symptom of both narcolepsy and OSA that contributes to the well-recognized burdens that are associated with these diseases, including patient-reported reductions in function, daily activities, and quality of life; increased risk of workplace and vehicular accidents; and a substantial impact on family and partners.[4–9]

There is currently no cure for narcolepsy. Furthermore, the treatment of excessive daytime sleepiness, the primary symptom, is based on pharmacologic management using medications from several classes, including the central nervous system depressant sodium oxybate, stimulants such as amphetamines, and the wake-promoting agents modafinil and armodafinil.[10–12] Treatment of OSA mainly relies on continuous positive airway pressure (CPAP) to reduce sleep-disordered breathing, and CPAP is currently considered the gold standard for OSA treatment. However, even among those who are adherent to CPAP, 12%–65% of individuals will still experience residual sleepiness,[13–16] which often requires additional treatment. This treatment may include the same wake-promoting agents and stimulants that are used for treating excessive daytime sleepiness in narcolepsy, although these medications can be associated with limitations that include suboptimal response, lack of tolerability, and potential for tolerance and abuse.[17,18]

Solriamfetol (JZP-110; [*R*]-2-amino-3-phenylpropylcarbamate hydrochloride) is a selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects.[19,20] Solriamfetol at daily doses of 75–300 mg is currently being evaluated for the reduction of sleepiness and improvement of wakefulness throughout the day in patients with narcolepsy and OSA. In Phase II trials in patients with narcolepsy, solriamfetol resulted in significant reductions compared with placebo in patient-reported excessive daytime sleepiness measured by using the Epworth Sleepiness Scale and significant increases in the ability to stay awake on the objective Maintenance of Wakefulness Test.[21,22]

In vitro studies have suggested that solriamfetol's effects seem to be distinct from those of traditional stimulants such as amphetamines.[20] At concentrations in the micromolar range, solriamfetol selectively bound to and inhibited reuptake at dopamine and norepinephrine transporters without promoting monoamine release; in transfected cells, the solriamfetol concentrations that resulted in 50% inhibition of dopamine and norepinephrine reuptake were 2.9 and 4.4 μM, respectively.[20]

Solriamfetol has high solubility and high permeability, and is considered a Biopharmaceutics Classification System class 1 compound. It is predominantly excreted unchanged in urine, with ≤1% of the dose recovered as the minor metabolite *N*-acetyl solrimafetol.[20] Consequently, solriamfetol elimination is not expected to be affected by cytochrome P450–related genetic polymorphism.

Because the presence of food can potentially change the bioavailability of a drug by various mechanisms such as delaying gastric emptying, changing gastrointestinal pH, and physically/chemically interacting with a dosage form/drug substance, it is especially important to determine whether the pharmacokinetic (PK) parameters of a new drug are affected by food intake.[23] Therefore, the purpose of the present study was to assess the potential impact of a high-fat, high-calorie breakfast on the relative bioavailability of a single dose of solriamfetol. Secondary goals were to further characterize the renal excretion of solriamfetol under fasting conditions and to evaluate the safety and tolerability of solriamfetol under fasting and fed conditions.

SUBJECTS AND METHODS

Study Design

This prospective, Phase I, open-label, single-dose, 2-way crossover study was designed to assess the effect of food on the PK parameters and the relative bioavailability of solriamfetol in accordance with US Food and Drug Administration recommendations for conducting PK studies evaluating food effects.[23] The study was conducted between May 13, 2016, and June 24, 2016, at a single site in the United States (Vince and Associates Clinical Research, Overland Park, Kansas). The protocol was approved by Midlands Independent Review Board (Overland Park, Kansas), and the study was conducted in accordance with the Declaration of Helsinki (third revision) and the International Conference on Harmonisation/Good Clinical Practice. All subjects provided written informed consent before participation.

The study was conducted on an inpatient basis at the clinic study site, with subjects remaining at the site through the last sampling time point, which was at 48 h after dosing in each treatment period. Only meals and snacks provided by the study unit could be consumed, and these were standardized for all subjects, who were also instructed to avoid strenuous physical activity throughout the study. Solriamfetol at a dose of 300 mg, which is the highest strength intended to be marketed, was manufactured in Switzerland as a film-coated, immediate-release tablet and was provided by the sponsor. Subjects were randomized to receive either a 300-mg dose of solriamfetol in the fasted condition followed by a 300-mg dose of solriamfetol in the fed condition, or the reverse schedule, with the 2 administrations separated by a washout period of at least 7 days. In the fasted condition, subjects received the dose orally with 240 mL of water after an overnight fast of at least 10 h and continued fasting for an additional 4 h after dosing. In the fed condition, subjects received the same dose taken orally with 240 mL of water 30 min after start of a standardized high-fat, high-calorie breakfast of ~800−1000 calories, of which ~50% of the total caloric content was fat.[23] This breakfast consisted of 2 large eggs, 2 pieces of white toast, a total of 4 teaspoons butter, 2 slices of thick cut pork bacon, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. Medication compliance was verified by visual inspection of each subject's mouth and hands.

Subjects

Study participants were healthy subjects aged 18−55 years, inclusive, with weight at least 52 kg for men and 45 kg for women, and with a body mass index between 19.0 and 30.0 kg/m^2, inclusive. Subjects were required to be nonusers of nicotine-containing products within the previous 3 months; have a hemoglobin value ≥11.0 g/dL for women or ≥12.0 g/dL for men (to ensure subject safety during multiple blood draws for PK samples); and have used a medically acceptable method of contraception for the previous 2 months with additional consent to use such contraception throughout the study period and 90 days after study completion. Female subjects were excluded if they were pregnant or lactating. Main exclusion criteria included, but were not limited to, history or presence of any disease or condition that could interfere with absorption, distribution, metabolism, or excretion of drugs; self-reported consumption of >600 mg of caffeine per day; history of any illness, physical finding, laboratory examination, or ECG finding that might confound the results or conduct of the study or pose a risk to the subject; history or presence of phenylketonuria or a hypersensitivity or idiosyncratic reaction to phenylalanine-derived products, or any excipient in the formulated drug products; and previous exposure to solriamfetol.

Bioanalytic and PK Evaluations

Blood samples of ~4 mL were collected during each treatment period at the prespecified time points of within 30 min predose and within a 5-min window at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, and 48 h postdose. All blood samples were collected in labeled K_2EDTA tubes by direct venipuncture or indwelling catheter and kept on ice until the samples were centrifuged (within 30 min of collection) at ~3000 rpm at 4 °C for 10 min. The plasma was then pipetted into polypropylene tubes for freezing and storage at −70 °C until analysis.

Aliquots (~1 mL) of the urine samples pooled from each collection interval (predose, 0−4, 4−8, 8−12, 12−24, and 24−48 h) were frozen and stored at −70 °C until analysis.

Analyses of plasma and urine samples for solriamfetol and urine samples for *N*-acetyl solriamfetol were performed at a central bioanalytical laboratory (KCAS, LLC, Shawnee, Kansas) by using validated methods. For plasma samples, after protein precipitation with methanol, derivatization was performed with propionic anhydride with subsequent separation by reversed-phase HPLC and detection with positive-ion TurboIonSpray MS/MS using the API-4000 LC/MS/MS system (Sciex, Framingham, Massachusetts). Separation of urine samples was also by reversed-phase HPLC, with positive-ion TurboIonSpray MS/MS detection using the API-3000 LC/MS/MS system (Sciex). The assay ranges were 8.42−4210 ng/mL for plasma and 0.210−84.2 μg/mL for urine solriamfetol, and 20.0−5000 ng/mL for urine *N*-acetyl solriamfetol.

Standard curve and quality control samples were generated by using internal standards (^{13}C-solriamfetol and ^{13}C−*N*-acetyl-solriamfetol) to monitor assay performance. For precision, the intra-assay results showed that the %CV at the lower limit of quantitation was 3.2%−6.0% for solriamfetol in plasma, 1.6%−5.6% for solriamfetol in urine, and

1.8%−2.9% for *N*-acetyl solriamfetol in urine; the corresponding intra-assay accuracies, expressed as percent bias, were 1.0% to 3.9%, −3.1% to 5.6%, and −8.3% to −5.4% at the lower limit of quantitation of the 3 samples, respectively.

Plasma PK parameters, calculated by using noncompartmental analysis through Phoenix WinNonlin 6.3 and Phoenix Connect 1.3.1 software (Certara, Princeton, New Jersey), included C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, apparent $t_{1/2}$, V_d/F, and CL/F. Urine PK parameters included the amount of drug excreted in urine overall; fraction of drug excreted unchanged in urine overall; and renal clearance (CL_R).

Statistical Analyses

Plasma and urine PK parameters were summarized according to condition by using descriptive statistics. For C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, natural log-transformed data were analyzed for differences between fed and fasted conditions by using an ANOVA model for a 2-period crossover design, including effects for sequence, subject within sequence, period, and treatment. Results were expressed as least squares means, and the ratios of geometric means between conditions (fed/fasted) and their 2-sided 90% CIs were determined. As specified by guidance from the US Food and Drug Administration, an absence of food effect on relative bioavailability was shown if the 90% CIs were within the predefined equivalence limits of 80%−125% for the fed/fasted ratios.[23]

Up to 32 subjects were planned for enrollment to ensure that at least 26 subjects completed both treatment periods and had evaluable PK data. A sample size of 26 subjects was estimated to provide at least 90% power for showing bioequivalence for both C_{max} and AUC, assuming within-subject SDs of 0.191 and 0.207 for C_{max} and AUC, respectively, and a ±5% difference between the fed and fasted conditions.

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

Tolerability

Tolerability was evaluated by the reporting of adverse events (AEs) regardless of causality for all subjects who took at least 1 dose of study medication. The AEs were summarized by using the Medical Dictionary for Regulatory Activities version 18.0 (PSI International Inc., Fairfax, Virginia) preferred term and were determined by spontaneous reporting by the subjects, as well as direct observation and the use of nonleading questions by the investigator. The relationship of AEs to the study drug was determined in the opinion of the clinical investigator as none, unlikely related, possibly related, or probably related. In addition to assessment of seriousness, AEs were graded in severity as mild, moderate, or severe on the basis of standard criteria.[24] Evaluation of tolerability also included standard clinical laboratory testing (chemistry, hematology, coagulation, and urinalysis), vital signs, and ECG assessment, as well as the Columbia−Suicide Severity Rating Scale.[25] These tolerability assessments were performed at screening, upon intake and exit from the clinical study site or early termination, and at predefined time points relative to dosing for assessment of ECG (2.5 h postdose) and vital signs (immediately before and at 2 and 24 h postdose).

RESULTS

Sample Population

Of the 75 subjects who were screened, 43 failed to meet entry criteria, and 32 subjects were enrolled. The demographic characteristics of the subjects who entered the study are summarized in Table I, and they show that the population was 50% female,

Table I. Demographic characteristics of all enrolled subjects ($n = 32$). Values are given as mean (SD) (range) unless otherwise indicated.

Variable	Value
Age, y	35.6 (11.8) (19−54)
Male	16 (50%)
Race	
Black	17 (53.1%)
White	15 (46.9%)
Ethnicity	
Hispanic/ Latino	3 (9.4%)
Non-Hispanic/ Latino	29 (90.6%)
Weight, kg	72.8 (11.6) (53.8−95.0)
Height, cm	169.5 (9.6) (154.0−190.5)
Body mass index, kg/m^2	25.3 (2.7) (19.5−29.9)

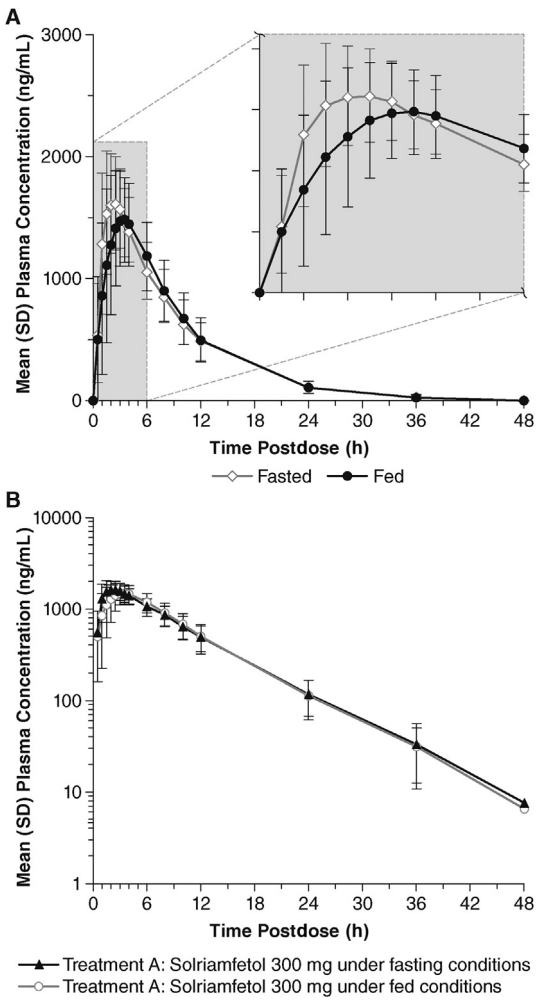

Fig. 1. Plasma concentration–time profiles after single-dose administration of 300-mg solriamfetol (n = 31). A) Linear scale (insert shows hours 0–6); B) log-transformed scale.

53.1% black, and 46.9% white, with a mean age of 35.6 years. All enrolled subjects took both doses, completed the study, and are included in the safety analysis. However, 1 subject did not consume 100% of the standardized high-fat, high-calorie breakfast before dosing and was excluded from the PK analysis.

Plasma PK Parameters

After administration of a single oral dose of 300-mg solriamfetol, there was rapid absorption under both fed and fasted conditions (Fig. 1), with similar mean plasma concentration–time profiles between the 2 administration conditions, although there was a 1-h delay in median T_{max} for the fed condition. Table II presents the PK parameters after solriamfetol administration and shows that mean solriamfetol C_{max} and $AUC_{0-\infty}$ values after the fed condition (1640 ng/mL and 16,783 ng h/mL) were ~6% and 2% lower, respectively, compared with the fasted condition (1740 ng/mL and 17,222 ng h/mL). The mean $t_{1/2}$ was similar between the fasted and fed conditions (6.1 and 5.9 h), respectively and median T_{max} was 3.0 h in the fed condition relative to 2.0 h with fasting. Values for CL/F and for V_d/F were similar between the 2 conditions.

An ANOVA revealed that the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ were close to 100%, and their 90% CIs were contained within the window of 80%–125% for the evaluated PK parameters of C_{max} (93.9%; 90% CI, 89.2–98.8), AUC_{0-t} (97.6%; 90% CI, 93.9–101.6), and $AUC_{0-\infty}$ (97.6%; 90% CI, 93.8–101.5) (Fig. 2).

Urine PK Parameters

As shown in Table III, solriamfetol was almost exclusively excreted in urine as unchanged drug when administered in the fasted condition, with an average of 89.8% of dose recovered in urine within the 48-h collection period. An additional 1.1% of solriamfetol was recovered as a minor metabolite, *N*-acetyl solriamfetol. The mean solriamfetol CL_R was 16.6 L/h, which constituted 90% of the overall clearance (CL/F, 18.4 L/h).

Safety and Tolerability

A total of 55 treatment-emergent AEs were reported for 18 subjects after dosing (56.3%), 27 in the fasted condition and 28 in the fed condition (Table IV); all AEs were considered by the investigators to be related or suspected to be related to study drug. The frequency and types of AEs were similar under fasted and fed conditions, consistent with similar solriamfetol exposures observed under the 2 conditions, and there were no serious AEs or study withdrawals due to AEs. All events were considered to be of mild severity, and all resolved with no sequelae and without the need for treatment. The most frequently reported AEs (>2 subjects with either treatment) were insomnia (11 subjects), headache, hypervigilance, decreased appetite

Table II. Plasma pharmacokinetic parameters after single-dose administration of solriamfetol 300 mg.

Parameter	Mean (SD), %CV	
	Fasted ($n = 31$)	Fed ($n = 31$)
C_{max}, ng/mL	1740 (423), 24.3	1640 (431), 26.2
$T_{max,}$ h*	2.0 (1.0–3.5)	3.0 (0.5–6.0)
AUC_{0-t}, ng h/mL	17,054 (4226), 24.8	16,628 (4062), 24.4
$AUC_{0-\infty}$, ng h/mL	17,222 (4225), 24.5	16,783 (4075), 24.3
$t_{1/2}$, h	6.1 (1.2), 20.3	5.9 (1.2), 19.6
V_d/F, L	158.2 (37.3), 23.6	159.8 (38.9), 24.4
CL/F, L/h	18.4 (4.2), 22.7	18.8 (4.2), 22.4

* Median (range).

(6 subjects each), and nausea (4 subjects). No clinically relevant abnormalities were observed for laboratory values, vital signs, or ECG, and there was no indication of suicidal ideation on the Columbia–Suicide Severity Rating Scale.

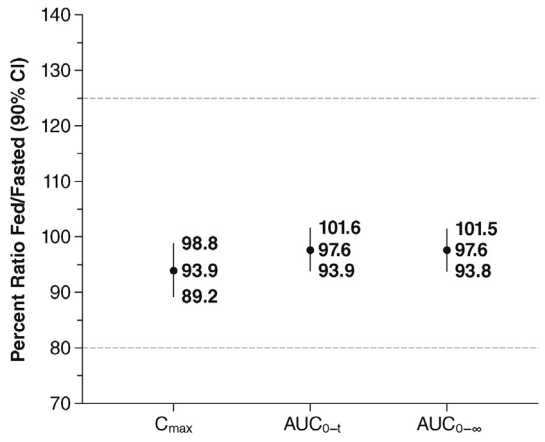

Fig. 2. Percent ratios and 90% CIs of the fed/fasted geometric mean values for the pharmacokinetic parameters of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} (log-transformed data). Data are from all subjects who completed the study ($n = 31$; one participant did not consume 100% of breakfast). A 90% CI for a given ratio within the predefined interval of 80%–125% (dotted lines) was considered to indicate bioequivalence.

DISCUSSION

To the best of our knowledge, this study is the first to report on the PK characteristics of solriamfetol, an investigational medication that has shown reductions in sleepiness and improvement of wakefulness in patients with narcolepsy[21,22] and which is being evaluated for the same indication in patients with OSA. After administration of a single, oral dose of 300-mg solriamfetol to healthy subjects, results showed that the drug was rapidly absorbed regardless of food intake, with total exposure that was similar in the fed and fasted conditions. In particular, the primary endpoint of the natural log-transformed PK parameters showed that the 90% CIs of the geometric mean ratios for both C_{max} and $AUC_{0-\infty}$ for the fed/fasted conditions were contained within the window of 80%–125%; that is, 90% CIs of 89.2–98.8 and 93.8–101.5 for C_{max} and $AUC_{0-\infty}$, respectively. These results indicate that there is no difference in the rate or extent of absorption between the fasted and fed conditions, and they support the administration of solriamfetol without regard to meals.[23] The observed lack of food effect is consistent with solriamfetol being a Biopharmaceutics Classification System class 1 compound (highly soluble, highly permeable), making the absorption of the rapidly dissolving immediate-release tablets less dependent on the gastrointestinal pH and location. Results from the Phase II clinical trial show that efficacy was observed ~1 h after

Table III. Urine pharmacokinetic parameters after single-dose administration of solriamfetol 300 mg in the fasted condition.

Parameter	Mean (SD), %CV	
	Solriamfetol	*N*-acetyl solriamfetol
A_e, mg	269.5 (27.4), 10.2	3.91 (2.8), 70.9
F_e, %	89.8 (9.1), 10.2	1.1 (0.8), 70.9
CL_R, L/h	16.6 (4.3), 26.0	—

A_e = drug excreted in urine overall; F_e = fraction of drug excreted unchanged in urine overall; CL_R = renal clearance.

dosing,[22] suggesting that the onset of action of solriamfetol occurs before T_{max} and consequently, the delay of 1 h in T_{max} after consumption of the high-fat, high-calorie breakfast likely has minimal clinical significance. The intersubject variability for solriamfetol C_{max} and $AUC_{0-\infty}$ was low (%CV, 24%–26%) and consistent with or without food.

After single-dose oral administration of 300-mg solriamfetol to healthy subjects in the fasted condition, the mean percentage of the solriamfetol dose recovered in urine as unchanged drug was 89.8%. Consistent with previous data, the present study also identified a minor metabolite of solriamfetol in the urine, *N*-acetyl solriamfetol, which constituted 1.1% of the solriamfetol dose.[20]

Table IV. Adverse events (AEs).

Event	No. (%)	
	Fasted (n = 32)	Fed (n = 32)
Any AE	13 (40.6)	14 (43.8)
Serious AEs	0	0
Withdrawal due to AEs	0	0
Treatment-related AEs	13 (40.6)	14 (43.8)
Most common AEs*		
Insomnia	7 (21.9)	7 (21.9)
Headache	5 (15.6)	4 (12.5)
Hypervigilance	3 (9.4)	4 (12.5)
Decreased appetite	3 (9.4)	3 (9.4)
Nausea	3 (9.4)	2 (6.3)

* Occurring with a frequency >2 subjects with either treatment.

In the safety and tolerability analysis, there were no serious AEs and no withdrawals due to AEs. In addition, no clinically relevant sequelae were attributable to the drug, and no trend was observed between treatment conditions with respect to the incidence or types of individual AEs. The most frequently reported AEs, insomnia, headache, hypervigilance, decreased appetite, and nausea, were all mild in severity and resolved without treatment. The occurrence of these AEs is similar to the most common AEs that have been reported in solriamfetol clinical trials.[21,22]

CONCLUSIONS

The present study demonstrated the bioequivalent relative bioavailability when a single therapeutic dose of 300-mg solriamfetol was taken with and without food. Solriamfetol can therefore be administered without food intake in the clinical setting. These data also show that renal excretion of unchanged solriamfetol is the primary route of elimination. The tolerability profile of solriamfetol in this single-dose study was consistent with what has been reported in larger clinical trials.

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CONFLICTS OF INTEREST

Dr. Zomorodi is an employee and Ms. Lu is a former employee of Jazz Pharmaceuticals; in the course of their employment, they have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. Dr. Kankam is an employee of Vince and Associates Clinical Research and provided consulting services to Jazz Pharmaceuticals for this study. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Jazz Pharmaceuticals provided funding to CRG for writing and editorial support. The authors including the Jazz Pharmaceuticals authors were involved with designing the study, collecting, analyzing, and interpreting the data, and writing the manuscript. Although Jazz Pharmaceuticals was involved in the review of the manuscript, the content of this manuscript, the ultimate interpretation, and the decision to submit it for publication in Clinical Therapeutics was made by the authors independently.

REFERENCES

1. Dauvilliers Y, Montplaisir J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology*. 2001;57:2029–2033.
2. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. *Sleep*. 2002;25:197–202.
3. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *J Thorac Dis*. 2015;7:1311–1322.
4. Dodel R, Peter H, Spottke A, et al. Health-related quality of life in patients with narcolepsy. *Sleep Med*. 2007;8:733–741.
5. Philip P, Sagaspe P, Lagarde E, et al. Sleep disorders and accidental risk in a large group of regular registered highway drivers. *Sleep Med*. 2010;11:973–979.
6. Black J, Reaven NL, Funk S, et al. The Burden of Narcolepsy Disease (BOND) study: healthcare utilization and cost findings. *Sleep Med*. 2014;15:522–529.
7. Hirsch Allen AJ, Bansback N, Ayas NT. The effect of OSA on work disability and work-related injuries. *Chest*. 2015;147:1422–1428.
8. Luyster FS. Impact of obstructive sleep apnea and its treatments on partners: a literature review. *J Clin Sleep Med*. 2017;13:467–477.
9. Maski K, Steinhart E, Williams D, et al. Listening to the patient voice in narcolepsy: diagnostic delay, disease burden, and treatment efficacy. *J Clin Sleep Med*. 2017;13:419–425.
10. Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. *Eur J Neurol*. 2006;13:1035–1048.
11. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30:1705–1711.
12. Keam S, Walker MC. Therapies for narcolepsy with or without cataplexy: evidence-based review. *Curr Opin Neurol*. 2007;20:699–703.
13. Gasa M, Tamisier R, Launois SH, et al. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res*. 2013;22:389–397.
14. Koutsourelakis I, Perraki E, Economou NT, et al. Predictors of residual sleepiness in adequately treated obstructive sleep apnoea patients. *Eur Respir J*. 2009;34:687–693.
15. Weaver TE, Maslin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30:711–719.
16. Pepin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J*. 2009;33:1062–1067.
17. Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med*. 2015;16:9–18.
18. Rosenberg RP. Recommended treatment strategies for patients with excessive daytime sleepiness. *J Clin Psychiatry*. 2015;76:e1330.
19. Hasan S, Pradervand S, Ahnaou A, Drinkenburg W, Tafti M, Franken P. How to keep the brain awake? The complex molecular pharmacogenetics of wake promotion. *Neuropsychopharmacol*. 2009;34:1625–1640.
20. Baladi MG, Forster MJ, Gatch MB, et al. Characterization of the neurochemical and behavioral effects of solriamfetol (JZP-110), a selective dopamine and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther*. 2018;366:367–376.
21. Bogan R, Feldman N, Emsellem HA, et al. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. *Sleep Med*. 2015;16:1102–1108.
22. Ruoff C, Swick T, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016;39:1379–1387.
23. US Food and Drug Administration. Guidance for industry. Food-effect bioavailability and fed bioequivalence studies. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf; 2002. Accessed December 18, 2018.

24. International Conference on Harmonisation. Guideline for industry. Clinical safety data management: definitions and standards for expedited reporting. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf; 1994. Accessed December 18, 2018.
25. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168:1266–1277.

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