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An Open-Label, Single-Dose, Phase 1 Study of the Pharmacokinetics and Safety of Solriamfetol (JZP-110) in Subjects With Normal or Impaired Renal Function and With End-Stage Renal Disease Requiring Hemodialysis

Presented at
2107 Annual Meeting of the American College of Clinical Pharmacology
September 17-19, 2017 • San Diego, CA

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Background

- Excessive sleepiness is a common symptom of narcolepsy and obstructive sleep apnea, both of which are characterized by well-recognized socioeconomic burdens[1-4]
- Solriamfetol (JZP-110) is a selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects
- In phase 3 trials, solriamfetol demonstrated improvements in wakefulness and excessive sleepiness in patients with narcolepsy and obstructive sleep apnea[5-7]
- Data from a clinical mass balance study have shown that urinary excretion is the major route of solriamfetol elimination[8]
  - At least 90% of drug is excreted unchanged within 48 hours
  - Solriamfetol undergoes minimal hepatic metabolism
- Since renal clearance is the primary route of elimination, it is important to determine how renal impairment affects the pharmacokinetic (PK) and safety profile of solriamfetol

Objective

- To evaluate the PK and safety of solriamfetol in subjects with different levels of renal impairment and in those undergoing hemodialysis in accordance with United States Food and Drug Administration guidance for PK studies in patients with impaired renal function[9]

Methods

- This open-label, single-dose study of solriamfetol was conducted at 2 sites in the United States between October and December 2015
- Subjects were men and women (18–80 years old) with body mass index (BMI) between 18 and 35 kg/m^2 who were categorized based on level of renal impairment according to estimated glomerular filtration rate (eGFR):
  - *Group 1:* Normal renal function (eGFR ≥90 mL/min/1.73 m^2)
  - *Group 2:* Mild renal impairment (eGFR 60–89 mL/min/1.73 m^2)
  - *Group 3:* Moderate renal impairment (eGFR 30–59 mL/min/1.73 m^2)
  - *Group 4:* Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
  - *Group 5:* End-stage renal disease (ESRD) requiring ≥3 hemodialysis treatments per week for the past 3 months
- Groups 1–4 received one 75-mg dose on Day 1
- Group 5 received one 75-mg dose on Day 1 (followed by 4-hour hemodialysis starting 2 hours post dose), and one 75-mg dose on Day 8 (without hemodialysis)
- All Groups: Serial blood (~4 mL) and urine samples were collected at pre-specified time points/intervals up to 48 or 72 hours post dose
- Group 5: Dialysate and pre- and post-dialyzer blood samples were collected on Day 1 before start of hemodialysis (2 hours post dose) and hourly up to 6 hours post dose
- Bioanalytical analyses were performed by a central laboratory (KCAS, LLC, Shawnee, KS)
  - Analyses measured solriamfetol in human plasma (range 8.42–4210 ng/mL), human urine (range 0.210–84.2 µg/mL), and human dialysate (range 1.68–842 ng/mL)
- PK parameters included area under plasma concentration-time curve from time 0 to last quantifiable concentration (AUC_{0-t}) and infinity ($AUC_{0-\infty}$); maximum concentration (C_{max}); time to C_{max} (T_{max}); elimination half-life ($t_{1/2}$); apparent oral clearance (CL/F); apparent volume of distribution (V_d/F); urinary excretion expressed as cumulative fraction of dose excreted unchanged in urine (CumFe); renal clearance (CL_R); cumulative fraction of the dose in dialysate ($CumF_D$; Group 5 only); and hemodialysis clearance (CL_D; Group 5 only)
- Differences in PK of Groups 2–5 relative to Group 1 were evaluated using a linear-effects model of the natural log-transformed PK parameters
  - Point estimates and 90% confidence interval (90% CI) for differences on the natural log scale were exponentiated to obtain estimates for ratios of geometric means
  - For Group 5, subjects were analyzed separately without hemodialysis on Day 8 (Group 5.1) and with hemodialysis on Day 1 (Group 5.2)
- Tolerability assessed as occurrence of treatment-emergent adverse events (TEAEs) regardless of causality, as well as assessment of vital signs and clinical laboratory tests

Results

- A total of 31 subjects were enrolled and received treatment, and 30 subjects completed the study
- Most subjects in Groups 1–4 were white; however, most subjects in Group 5 were black or African American (**Table 1**)
  - Mean ages for Groups 1–4 were comparable
  - Mean BMIs were comparable across all groups
  - All subjects in Group 1 matched the mean age (within±10 years) and BMI (within±20%) of subjects in Groups 2–5 (mean age, 59.2 years and BMI, 28.3 kg/m^2)

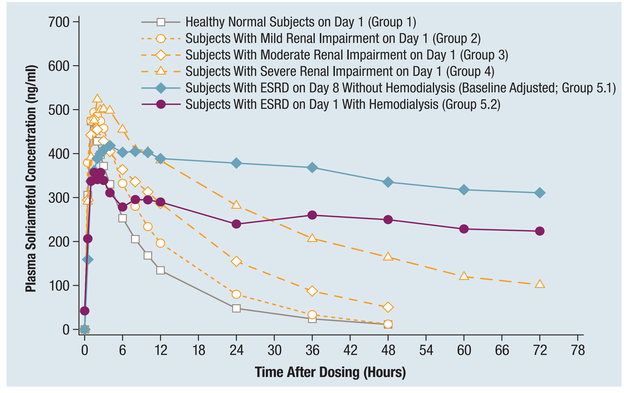
Table 1. Demographic Characteristics of the Study Population

Variable		Group 1: Normal (n=6)	Renal Impairment			
			Group 2: Mild (n=6)	Group 3: Moderate (n=6)	Group 4: Severe (n=6)	Group 5: ESRD (n=7)
Sex, n (%)	Female	3 (50)	4 (67)	2 (33)	2 (33)	2 (29)
	Male	3 (50)	2 (33)	4 (67)	4 (67)	5 (71)
Race, n (%)	White	5 (83)	5 (83)	4 (67)	5 (83)	1 (14)
	Black or African American	1 (17)	1 (17)	2 (33)	1 (17)	6 (86)
Ethnicity, n (%)	Non-Hispanic or Latino	0	3 (50)	2 (33)	3 (50)	6 (86)
	Hispanic or Latino	6 (100)	3 (50)	4 (67)	3 (50)	1 (14)
Age, mean±SD, y		55.8±3.9	67.8±7.4	70.2±7.7	59.7±15.6	42.0±7.6
BMI, mean±SD, kg/m^2		28.1±2.7	25.1±4.1	28.8±1.9	29.3±3.0	29.9±3.0
eGFR, mean±SD, mL/min/1.73 m^2		111.8±32.3	78.5±8.4	44.2±6.2	16.2±5.8	7.4±4.8

BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SD, standard deviation.

- In Groups 1–4 (Table 2):
  - Mean C_{max} and T_{max} did not substantially vary across Groups 1–4 (**Figure 1** and **Table 2**)
  - Total exposure (AUC) increased with greater renal impairment (**Figure 1** and **Table 2**)
  - $t_{1/2}$ was 1.2-, 1.9-, and 3.9-fold higher in Groups 2, 3, and 4, respectively, relative to Group 1
  - Renal excretion of unchanged solriamfetol (CumFe) decreased with greater levels of renal impairment
  - The decrease in solriamfetol clearance was proportional to the decrease in eGFR

Figure 1. Mean Plasma Solriamfetol Concentrations Over Time



ESRD, end-stage renal disease.

- In Group 5 (**Table 2**):
  - AUC was higher, C_{max} was slightly lower, and $t_{1/2}$ was >100 hours, compared with Group 1
  - Hemodialysis removed 20.6% of solriamfetol dose as unchanged drug with clearance of 12.4 L/h

Table 2. Solriamfetol PK Parameters Following a Single 75-mg Dose[a]

Variable	Group 1: Normal (n=6)	Renal Impairment			ESRD (Group 5)	
		Group 2: Mild (n=6)	Group 3: Moderate (n=6)	Group 4: Severe (n=6)	Group 5.1 (Baseline Adjusted): Without Hemodialysis (on Day 8) (n=6)[b]	Group 5.2: With Hemodialysis (on Day 1) (n=7)[c]
C_{max}, ng/mL	499.0±142.4 (28.5)	521.8±118.8 (22.8)	517.3±131.6 (25.4)	552.8±154.4 (27.9)	474.1±79.0 (16.7)	396.4±75.4 (19.0)
T_{max}, median (range), h	1.3 (0.5, 2.0)	1.5 (0.5, 2.0)	1.5 (1.0, 2.5)	2.0 (0.5, 3.0)	3.3 (1.0, 24.0)	1.5 (1.5, 10.0)
$t_{1/2}$, h	7.6±5.1 (67.7)	9.1±1.6 (18.1)	14.3±4.5 (31.4)	29.6±14.4 (48.7)	100.5±78.8 (78.4)[e]	164.7±81.4 (49.4)[f]
AUC_{0-t}, ng·h/mL[d]	4,849±3,454 (71.2)	6,613±1,574 (23.8)	9,230±2,538 (27.5)	17,500±9,267 (52.9)	25,580±4,544 (17.8)	18,920±3,131 (16.5)
$AUC_{0-\infty}$, ng·h/mL	5,273±4,104 (77.8)	6,836±1,730 (25.3)	10,470±3,642 (34.8)	23,650±16,776 (70.9)	64,560±35,962 (55.7)[e]	76,770±41,993 (54.7)[e]
CL/F, L/h	19.8±10.1 (50.9)	11.5±2.5 (22.1)	7.8±2.4 (30.5)	4.7±2.8 (59.4)	1.6±1.1 (72.3)[e]	1.5±1.3 (91.0)[f]
V_d/F, L	163.9±23.8 (14.5)	147.2±29.1 (19.8)	152.0±32.6 (21.4)	157.2±41.2 (26.2)	153.6±45.6 (29.7)[e]	231.4±28.5 (12.3)[f]
CumFe, %[d]	85.8±7.7 (9.0)	80.0±9.0 (11.2)	66.4±12.8 (19.2)	64.0±17.7 (27.7)	52.9	42.1
CL_R, L/h	17.0±7.7 (45.4)	9.3±1.6 (17.1)	5.8±2.0 (34.1)	3.8±2.6 (68.0)	—	—
$CumF_D$, %	—	—	—	—	—	20.6±1.7 (8.4)
CL_D, L/h	—	—	—	—	—	12.4±1.5 (12.5)

[a]All values are mean±standard deviation (% coefficient of variation) unless otherwise noted; [b]One subject from Group 5 discontinued the study before Day 8 due to adverse events of mild elevated alanine aminotransferase and aspartate aminotransferase; [c]Excluding 2 concentration values: 1 subject at pre-dose and 1 subject at 24 hours; [d]Over 48 hours for Groups 1–3 and over 72 hours for Groups 4 and 5; [e]n=3; [f]n=6. AUC, area under plasma concentration-time curve; AUC_{0-t}, AUC from time 0 to last quantifiable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; C_{max}, maximum concentration; CL_D, hemodialysis clearance; CL_R, renal clearance; $CumF_D$, cumulative fraction of dose in dialysate; CumFe, urinary excretion expressed as cumulative fraction of dose excreted unchanged in urine; ESRD, end-stage renal disease; PK, pharmacokinetic; T_{max}, time to C_{max}; $t_{1/2}$, elimination half-life.

- Based on geometric mean ratios of Groups 2–4 relative to Group 1 (Table 3):
  - C_{max} values were generally similar, with the greatest increase, 11%, in Group 4
  - Total exposure ($AUC_{0-\infty}$) increased by 53% (1.53-fold), 129% (2.29-fold), and 339% (4.39-fold) in Groups 2, 3, and 4, respectively
- Based on geometric mean ratios of Group 5 relative to Group 1, AUC0-t increased 357% with hemodialysis (4.57-fold; Group 5.2) and 518% without hemodialysis (6.18-fold; Group 5.1) versus Group 1 (Table 3)
- After hemodialysis (Group 5.2), solriamfetol AUC0-t and Cmax values were approximately 26% and 17% lower, respectively, relative to without hemodialysis (Group 5.1; Table 3)

Table 3. Statistical Comparisons of Solriamfetol Plasma PK Parameters

PK Parameter	Group 1: Normal (n=6)	Renal Impairment			ESRD (Group 5)	
		Group 2: Mild (n=6)	Group 3: Moderate (n=6)	Group 4: Severe (n=6)	Group 5.1 (Baseline Adjusted): Without Hemodialysis (on Day 8) (n=6)[a]	Group 5.2: With Hemodialysis (on Day 1) (n=7)[a]
Geometric LS means						
C_{max}, ng/mL	482.3	510.5	503.2	533.0	468.8	389.9
AUC_{0-t}, ng·h/mL	4,087.3	6,469.6	8,960.2	15,549	25,253	18,689
$AUC_{0-\infty}$, ng·h/mL	4,363.9	6,672.4	10,002	19,140	56,319[c]	65,306[d]
Percent ratio (90% CI) of geometric mean relative to Group 1						
C_{max}, ng/mL	—	105.9 (80.6–139.0)	104.3 (78.4–138.9)	110.5 (81.1–150.6)	97.2 (76.1–124.1)	80.9 (63.4–103.1)
AUC_{0-t}, ng·h/mL	—	158.3 (97.5–256.9)	219.2 (133.7–359.6)	380.4 (208.4–694.4)	617.8 (385.3–990.8)	457.2 (296.6–704.9)
$AUC_{0-\infty}$, ng·h/mL	—	152.9 (92.9–251.7)	229.2 (135.6–387.4)	438.6 (217.3–885.3)	1,290.6 (542.8–3068.5)	1,496.5 (748.7–2991.2)

[a]One subject from Group 5 discontinued the study before Day 8 due to adverse events of mild elevated ALT and AST; [b]Excluding 2 concentration values: 1 subject at pre-dose and 1 subject at 24 hours; [c]n=3; [d]n=6. ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under plasma concentration-time curve; AUC0-t, AUC from time 0 to last quantifiable concentration; AUC0-∞, AUC from time 0 to infinity; Cmax, maximum concentration; CI, confidence interval; LS, least squares; PK, pharmacokinetic.

- Five TEAEs were reported in 4 subjects (13%; **Table 4**)
  - There were no deaths or serious TEAEs
  - TEAEs included single events of headache, nausea, and skin abrasion; all were mild in severity
  - One subject discontinued in Group 5 due to increased alanine aminotransferase and aspartate aminotransferase 6 days after dosing, which resolved on Day 11
    - These events were considered mild and related, or suspected to be related, to study drug; no other TEAEs were reported for this subject

Table 4. Treatment-Emergent Adverse Events

Adverse Event	Number (%) of Subjects (N=31)					
	Group 1: Normal (n=6)	Renal Impairment			ESRD (Group 5)	
		Group 2: Mild (n=6)	Group 3: Moderate (n=6)	Group 4: Severe (n=6)	Group 5.1: Without Hemodialysis (on Day 8) (n=6)[a]	Group 5.2: With Hemodialysis (on Day 1) (n=7)
Any TEAE	0	1 (17)	1 (17)	0	1 (17)	1 (14)
Discontinuation due to TEAEs	0	0	0	0	0	1 (14)
Nausea	0	0	0	0	1 (17)	0
Skin abrasion	0	1 (17)	0	0	0	0
ALT increased	0	0	0	0	0	1 (14)
AST increased	0	0	0	0	0	1 (14)
Headache	0	0	1 (17)	0	0	0

[a]One subject from Group 5 discontinued the study before Day 8 due to adverse events of mild elevated ALT and AST.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESRD, end-stage renal disease; TEAEs, treatment-emergent adverse events.

Conclusions

- Following single-dose administration and consistent with renal clearance being the primary route of elimination for solriamfetol:
  - Solriamfetol $t_{1/2}$ and total exposure (AUC) increased and urinary excretion decreased with increasing renal impairment, while C_{max} was essentially unchanged
  - Solriamfetol clearance was approximately proportional to renal function
- Solriamfetol was partially cleared through hemodialysis
- No new safety concerns were identified for solriamfetol

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Support

This study was supported by Jazz Pharmaceuticals. In 2014, Jazz Pharmaceuticals plc acquired a world-wide license (except in certain countries in Asia) to develop and commercialize solriamfetol from SK Biopharmaceuticals, who discovered the compound. Under the direction of the authors,
E. Jay Bienen, PhD, of The Curry Rockefeller Group, LLC (CRG), provided medical writing assistance for this poster. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by CRG. Jazz Pharmaceuticals provided funding to CRG for writing and editorial support. Additional medical writing support was provided by Teresa L Steininger, PhD, CMPP at Jazz Pharmaceuticals.

Disclosures

KZ, DC, LL, and TL are employees of Jazz Pharmaceuticals who, in the course of their employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. KL has received research funding from Jazz Pharmaceuticals. TM has nothing to report.