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Effects of Solriamfetol on Cognitive Function in Participants With Cognitive Impairment Associated With Excessive Daytime Sleepiness in Obstructive Sleep Apnea: Results of the SHARP Study

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Introduction

- Excessive daytime sleepiness (EDS) is a common symptom of obstructive sleep apnea (OSA) and has been reported to persist in 10%–28% of patients despite treatment with continuous positive airway pressure (CPAP)[1-4]
- Cognitive impairment is a burdensome symptom in many patients with EDS associated with OSA and may involve performance deficits in several cognitive domains[4,5]
  - Impaired cognitive function can persist in patients despite CPAP therapy[4]
- Solriamfetol (Sunosi®) is a dopamine and norepinephrine reuptake inhibitor approved in the United States and European Union to treat EDS associated with OSA (37.5–150 mg/day)[6,7]
  - Preclinical evidence has demonstrated that solriamfetol activates trace amine-associated receptor 1 (TAAR1)[8]
  - TAAR1 agonism has emerged as a potential pharmacological target to improve cognitive function[9]

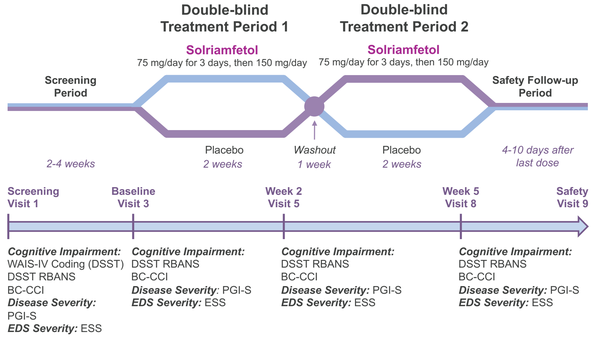
Objective

- The SHARP study aimed to assess whether solriamfetol improves cognitive function in patients with EDS associated with OSA and extant impaired cognition

Methods

- SHARP was a phase 4, multicenter, randomized, double-blind, placebo-controlled, 2-period crossover trial (NCT04789174) conducted from May 17, 2021, to September 19, 2022, across 28 sites in North America and Europe
- Participants were adult males and females aged 18–65 years diagnosed with OSA with associated EDS and impaired cognitive function
- Key inclusion criteria were EDS (Epworth Sleepiness Scale [ESS][10] score >10), impaired cognitive function (age-corrected scaled score ≤8 on Wechsler Adult Intelligence Scale Coding subtest [Digit Symbol Substitution Test, DSST] and ≥9 on British Columbia Cognitive Complaints Inventory [BC-CCI][11,12]), OSA therapy (CPAP use on ≥5 nights/week for ≥1 month prior to baseline, or no current CPAP therapy for ≥1 month prior to baseline but a history of attempted CPAP use for ≥1 month with ≥1 adjustment, or history of surgery intended to treat OSA symptoms)
- Key exclusion criteria were diagnosis of another sleep disorder, use of CPAP machine without ability to download adherence data, usual bedtime later than 1:00 AM, nighttime employment or variable shift work
- Primary endpoint: change from baseline to the end of each double-blind treatment period in the average score on the Coding Subtest (a variation of the DSST) of the Repeatable Battery for the Assessment of Neuropsychological Status (DSST RBANS); the average DSST RBANS score refers to the average of scores at 2, 4, 6, and 8 hours after an initial practice test (baseline) or postdose (postbaseline)
- Secondary endpoints: changes from baseline in BC-CCI and ESS scores at the end of each double-blind treatment period

Figure 1. SHARP Study Design



BC-CCI, British Columbia Cognitive Complaints Inventory; DSST, Digit Symbol Substitution Test; DSST RBANS, the Coding Subtest (a variation of the DSST) of the Repeatable Battery for the Assessment of Neuropsychological Status; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; PGI-S, Patient Global Impression of Severity; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition.

- Safety and tolerability: treatment-emergent adverse events (TEAEs)
- Data were analyzed with a repeated-measures regression model estimating treatment effects with baseline DSST RBANS scores as a covariate and controlling for period, sequence, and subject
  - Effect sizes (Cohen's *d*) were determined for primary and secondary endpoints

Results

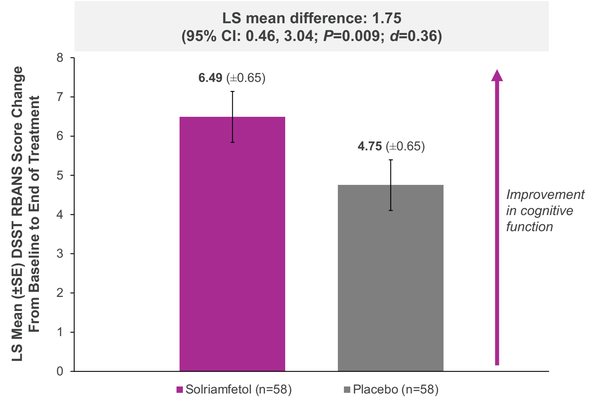
Table 1. Baseline Demographic and Clinical Characteristics

	Solriamfetol/ placebo (n=30)	Placebo/ solriamfetol (n=29)	Overall (N=59)
Age, years, mean (SD)	52.5 (10.5)	51.9 (11.1)	52.2 (10.7)
Sex, female, n (%)	10 (33.3)	11 (37.9)	21 (35.6)
Race, n (%)			
White	24 (80.0)	19 (65.5)	43 (72.9)
Black or African American	4 (13.3)	8 (27.6)	12 (20.3)
Asian	1 (3.3)	2 (6.9)	3 (5.1)
Unknown	1 (3.3)	0	1 (1.7)
BMI (kg/m^2), mean (SD)	32.8 (4.7)	31.6 (4.0)	32.2 (4.4)
DSST,[a] mean (SD)	6.6 (1.3)	6.9 (0.8)	6.8 (1.1)

[a]Age-corrected scaled score.
BMI, body mass index; DSST, Digit Symbol Substitution Test; SD, standard deviation.

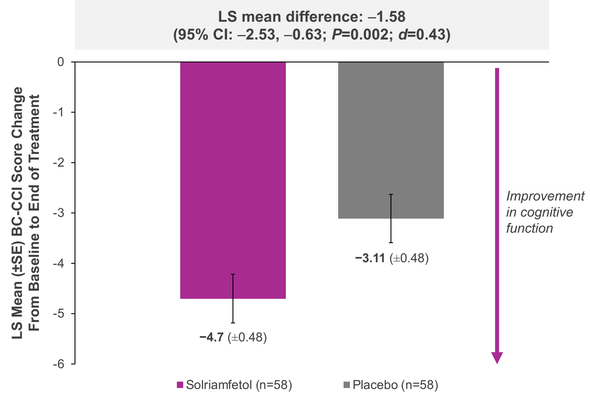
- Of 173 participants screened, 59 were enrolled and randomly assigned to 1 of the 2 treatment sequences; 57 participants completed the study

Figure 2. Overall DSST RBANS Scores Improved After Solriamfetol Treatment Compared With Placebo



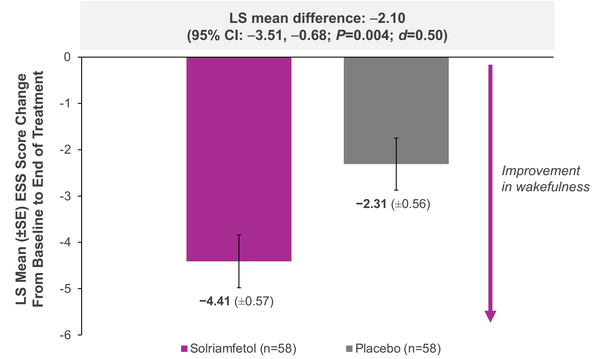
Data values above chart represent LS mean difference between solriamfetol and placebo (ie, solriamfetol - placebo).
CI, confidence interval; DSST, Digit Symbol Substitution Test; DSST RBANS, the Coding Subtest (a variation of the DSST) of the Repeatable Battery for the Assessment of Neuropsychological Status; LS, least squares; SE, standard error.

Figure 3. BC-CCI Scores Improved After Solriamfetol Treatment Compared With Placebo



Data values above chart represent LS mean difference between solriamfetol and placebo (ie, solriamfetol - placebo).
BC-CCI, British Columbia Cognitive Complaints Inventory; CI, confidence interval; LS, least squares; SE, standard error.

Figure 4. ESS Scores Improved After Solriamfetol Treatment Compared With Placebo



Data values above chart represent LS mean difference between solriamfetol and placebo (ie, solriamfetol - placebo).
CI, confidence interval; ESS, Epworth Sleepiness Scale; LS, least squares; SE, standard error.

Table 2. Treatment-Emergent Adverse Events[a]

n (%)	Solriamfetol (n=58)	Placebo (n=58)
Any TEAE	11 (19)	6 (10)
Nausea	4 (7)	1 (2)
Anxiety	2 (3)	0
Insomnia	1 (2)	1 (2)
Nasopharyngitis	1 (2)	1 (2)

[a]Reported by ≥2 participants.
TEAE, treatment-emergent adverse event.

- All TEAEs were mild or moderate in severity
- There were no deaths, serious TEAEs, or TEAEs that led to discontinuation of the study
- No suicidal thoughts or behaviors as determined by the Columbia Suicide Severity Rating Scale were reported

Conclusions

- Solriamfetol (150 mg/day) demonstrated improvement on objective and subjective measures of cognitive function and reduced subjective sleepiness in patients with cognitive impairment associated with OSA and EDS
- The safety profile of solriamfetol was consistent with prior studies
- The results confirm and expand on findings from previous studies that solriamfetol improves EDS in patients with OSA

References: **1.** Gasa M, et al. *J Sleep Res.* 2013;22(4):389-97. **2.** Pepin JL, et al. *Eur Respir J.* 2009;33(5):1062-7. **3.** Bonsignore MR, et al. *Front Neurol.* 2021;12:690008. **4.** Zhou J, et al. *Sleep Med.* 2016;23:99-108. **5.** Vasudev P, et al. *Indian J Sleep Med.* 2020;15(4):55-9. **6.** Sunosi® (solriamfetol) tablets [prescribing information]. New York, NY: Axsome Therapeutics, Inc; 2022. **7.** Sunosi™ (solriamfetol) tablets [summary of product characteristics]. European Medicines Agency; 2022. **8.** Gursahani H, et al. *Sleep.* 2022;45(suppl 1):A329. **9.** Alnefeesi Y, et al. *Neurosci Biobehav Rev.* 2021;131:192-210. **10.** Johns MW. *Sleep.* 1991;14(6):540-5. **11.** Jaeger J. *J Clin Psychopharmacol.* 2018;38(5):513-9. **12.** Iverson GL, Lam RW. *Ann Clin Psychiatry.* 2013;25(2):135-40.

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Disclosures: **H.P.A. Van Dongen** serves as a consultant to Jazz Pharmaceuticals. **E.B. Leary** is a current employee of Axsome Therapeutics and was a former employee of Jazz Pharmaceuticals at the time the study was conducted. **C. Drake** has nothing to disclose. **R. Bogan** serves as a consultant to Axsome Therapeutics, Avadel, Harmony, Jazz Pharmaceuticals, and Takeda and serves on speakers bureaus for Axsome Therapeutics, Harmony, Jazz Pharmaceuticals, and Idorsia. **J. Jaegar** is an employee of Cognition Metrics, LLC; Cognition Metrics received research support from Jazz Pharmaceuticals and Axsome Therapeutics. **R. Rosenberg** serves as a consultant to Jazz Pharmaceuticals and Axsome Therapeutics. **C. Streicher, H. Kwak, J. Bates, H. Tabuteau** are employees of Axsome Therapeutics.