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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

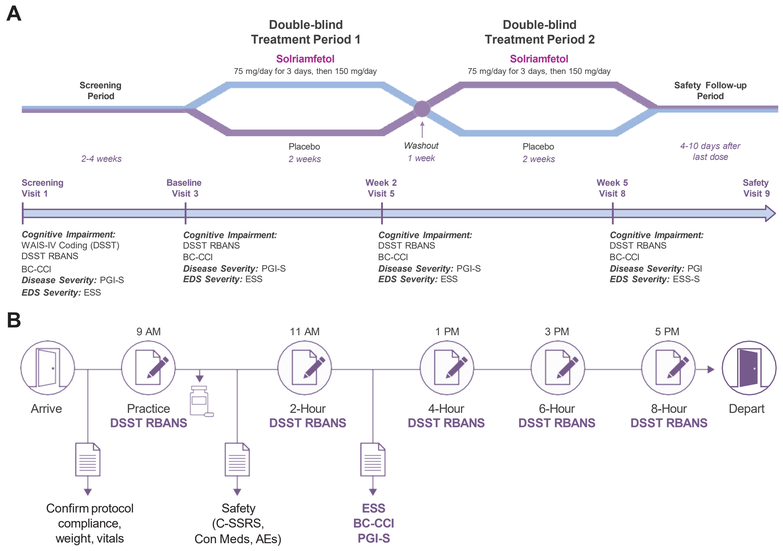
- Obstructive sleep apnea (OSA) is a common disorder characterized by repeated intermittent airway collapse resulting in disrupted sleep and excessive daytime sleepiness (EDS)[1]
  - Positive airway pressure (PAP) therapy reduces hypoxic events and mitigates sleep disruption, but EDS can persist in 10%–28% of patients despite PAP use[2-4]
- Cognitive impairment is a common, burdensome symptom in many patients with EDS associated with OSA[1,5] and can persist in some patients despite PAP therapy[1]
- Solriamfetol (Sunosi®) is a dopamine and norepinephrine reuptake inhibitor approved for use in adults in the United States and European Union for the treatment of EDS associated with OSA (37.5–150 mg/day)[6,7]
  - Preclinical evidence suggests solriamfetol improves aspects of cognition (eg, memory) in a murine model of sleep fragmentation[8]
  - Solriamfetol has been shown to activate trace amine-associated receptor 1 (TAAR1), which is a potential target to improve cognitive functions[9,10]

Objective

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

Methods

Figure 1. (A) Study Design and (B) Clinical Visit Structure



AEs, adverse events; BC-CCI, British Columbia Cognitive Complaints Inventory; Con Meds, concomitant medications; C-SSRS, Columbia-Suicide Severity Rating Scale; 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.

- SHARP was a phase 4, 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 adults aged 18–65 years diagnosed with OSA with associated EDS and impaired cognitive function
- Key inclusion criteria were: EDS (Epworth Sleepiness Scale[11] score >10), impaired cognitive function (age-corrected scaled score ≤8 on Wechsler Adult Intelligence Scale Coding subtest of the Digit Symbol Substitution Test [DSST] and ≥9 on British Columbia Cognitive Complaints Inventory [BC-CCI][12,13]), OSA therapy (PAP use on ≥5 nights/week for ≥1 month prior to baseline, or no current PAP therapy for ≥1 month prior to baseline but a history of attempted PAP 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 PAP 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 measured at 2, 4, 6, and 8 hours after an initial practice test (baseline) or postdose (postbaseline)
- Secondary endpoints: changes from baseline to the end of each double-blind treatment period in DSST RBANS scores at each corresponding 2-, 4-, 6-, and 8-hour postdose time points, overall BC-CCI scores, and overall Patient Global Impression of Severity (PGI-S) scores (related to problems with concentration, memory, and thinking skills over the last week; severity is scored by participants using a 5-point Likert-type scale, with scores ranging from 0 ["none"] to 4 ["very severe"])
- 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

Results

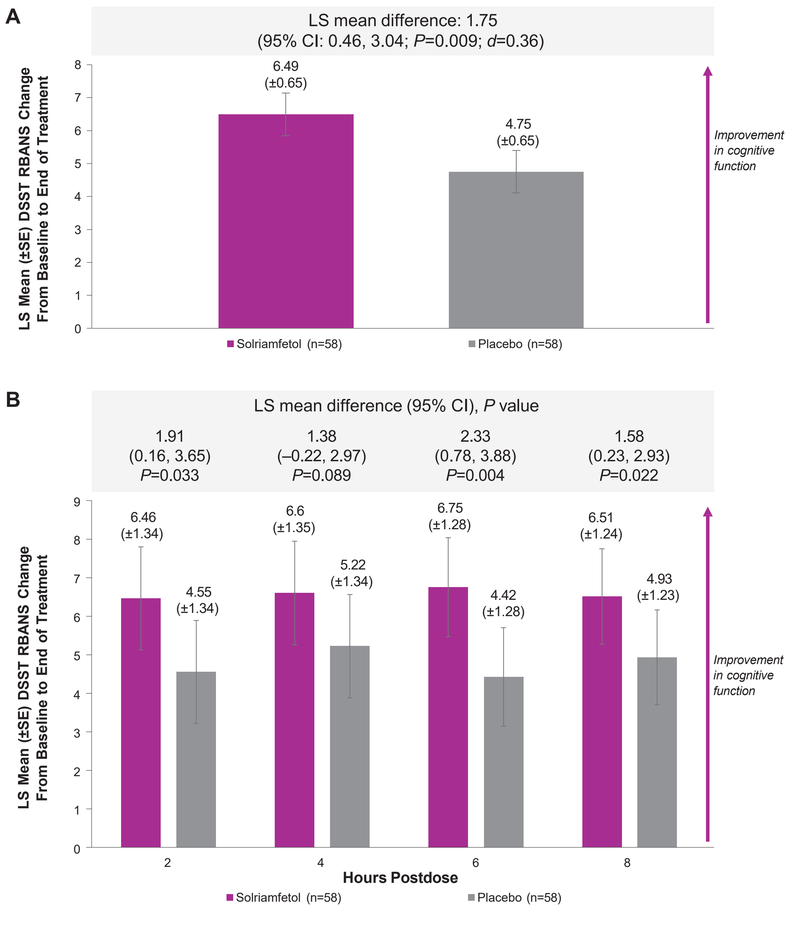
Table 1. Baseline Demographic and Clinical Characteristics

	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)
BC-CCI, mean (SD)	11.4 (2.5)	11.4 (2.5)	11.4 (2.5)
PGI-S,[b] mean (SD)	2.2 (0.8)	2.3 (0.7)	2.3 (0.7)
PAP use, n (%)	22 (73)	20 (69)	42 (71)
Adherent PAP use,[c] n (%)	18 (60)	16 (55)	34 (58)
Hours of PAP use,[d] mean (SD)	6.0 (2.4)	6.6 (2.7)	6.3 (2.5)

[a]Age-corrected scaled score. [b]Specifically related to perceived cognitive function, including concentration, memory, and thinking skills. [c]Adherent PAP use defined as ≥4 hours of PAP therapy a night for 70% of nights in any given timeframe. [d]Among all PAP users.
BC-CCI, British Columbia Cognitive Complaints Inventory; BMI, body mass index; DSST, Digit Symbol Substitution Test; PAP, positive airway pressure; PGI-S, Patient Global Impression of Severity; SD, standard deviation.

- Of 173 participants screened for this study, 59 were enrolled and randomly assigned to 1 of the 2 treatment sequences, and 57 completed the study
- At baseline, most participants were adherent to PAP, and average use among all PAP users was ≥6 hours per night

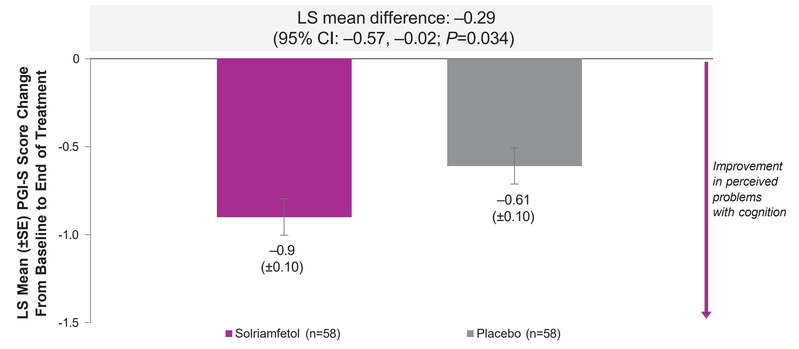
Figure 2. DSST RBANS Scores Improved (A) on the Primary Endpoint and (B) at 2, 6, and 8 Hours Postdose After Solriamfetol Treatment Compared With Placebo



Data values above charts 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.

- Solriamfetol significantly improved objective cognitive function overall (as an average of DSST RBANS scores; effect size *d*=0.36), and at each 2, 6, and 8 hours after dosing when compared with placebo

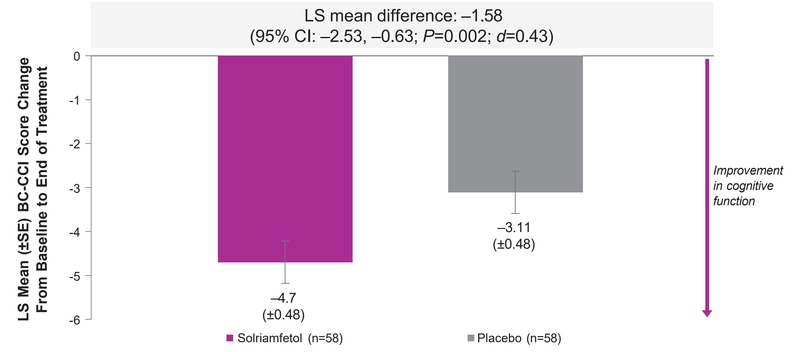
Figure 3. PGI-S Scores Improved After Solriamfetol Treatment Compared With Placebo



The PGI-S is a 5-item Likert-type scale for which participants rated the level of severity of their problems with concentration, memory, and thinking skills during the past 7 days; scores range from 0 (none) to 4 (very severe). A negative change from baseline indicates improvement in perceived cognitive function. Data value above bar chart represents LS mean difference between solriamfetol and placebo (ie, solriamfetol − placebo).
CI, confidence interval; PGI-S, Patient Global Impression of Severity; LS, least squares; SE, standard error.

- Solriamfetol led to an approximately 1-category improvement in the severity of perceived problems with cognitive function compared with an approximate one-half category change with placebo

Figure 4. BC-CCI Scores Improved After Solriamfetol Treatment Compared With Placebo



Data value above chart represents 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.

- Solriamfetol significantly improved ESS scores compared with placebo (least squares mean difference: −2.10 [95% CI: −3.51, −0.68; *P*=0.004; *d*=0.50])

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

Conclusions

- Solriamfetol (150 mg/day) improved objective and subjective cognition as measured by the DSST RBANS and BC-CCI, respectively, and reduced participants' perceived severity of cognitive impairment in patients with cognitive impairment associated with OSA and EDS
- The adverse event profile and high study completion rate suggest solriamfetol was well tolerated
- These data demonstrate that in patients with OSA-associated EDS and impaired cognition, solriamfetol provided sustained improvement in cognitive performance

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