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Solriamfetol Improves Cognitive Performance in Preclinical Models of Sleep Apnea and in a Randomized Placebo-Controlled Study of Sleep Apnea Participants (SHARP)

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Introduction

- Obstructive sleep apnea (OSA) is a disorder characterized by repeated intermittent hypoxic and arousal events resulting in fragmented sleep and excessive daytime sleepiness (EDS)[1]
  - Although positive airway pressure can reduce hypoxic events and mitigate sleep disruption, EDS often persists[2-4]
- Cognitive impairment is commonly associated with OSA and EDS and can lead to deficits across various domains, including memory, attention, and executive function[1,5,6]
- Solriamfetol (Sunosi®) is a dopamine-norepinephrine reuptake inhibitor (DNRI) with agonistic properties at the trace amine-associated receptor 1 (TAAR1) and serotonin 1A (5-HT_{1A}) receptors;[7,8] it is approved for use in adults in the United States, Canada, and select countries in Europe for the treatment of EDS associated with OSA (37.5–150 mg/day)[9,10]
- TAAR1 is a G-protein coupled receptor with affinity for the trace amines, and TAAR1 agonists have demonstrated pro-cognitive and wake-promoting effects in rodents and primates[11,12]

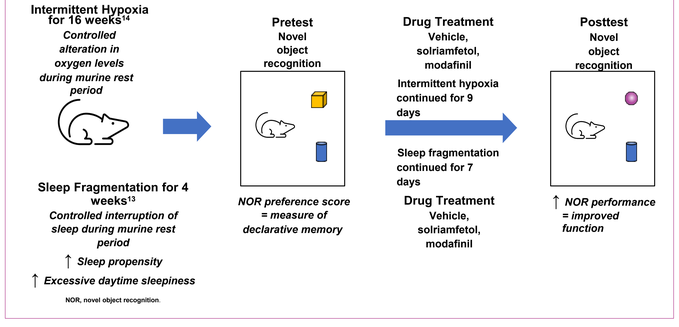
Objective

- We characterized *in vitro* binding and function of solriamfetol at relevant receptors and transporters, and hypothesized that solriamfetol will benefit declarative memory performance in murine models and cognition in a randomized clinical trial of cognitive impairment associated with EDS in OSA

Methods

- *In vitro* binding and functional studies were conducted in a panel of cell lines or membrane preparations expressing transmembrane receptors and monoamine transporters, including human dopamine and norepinephrine transporters (hDAT, hNET, respectively), human TAAR1 (hTAAR1), and 5-HT_{1A} to measure the activity of solriamfetol
- In preclinical studies,[13,14] mice were exposed to chronic intermittent hypoxia or sleep fragmentation protocols that model key aspects of OSA and are known to induce deficits in cognitive tasks[15]
  - Mice were administered equipotent doses of solriamfetol (200 mg/kg), modafinil (200 mg/kg), or vehicle; novel object recognition (NOR) task and elevated plus maze test (EPMT) were used to assess memory and anxiety-like behaviors, respectively
- SHARP (NCT04789174) was a phase 4, randomized, double-blind, placebo-controlled, crossover trial conducted in 59 adult participants with impaired cognition associated with OSA and EDS
  - All patients received solriamfetol (75 mg/day for 3 days followed by 150 mg/day) for 2 weeks, and placebo for 2 weeks, with treatment periods separated by a 1-week washout
  - Primary endpoint: Change from baseline to the end of each treatment period in the Coding Subtest (a variation of the Digit Symbol Substitution Test [DSST]) of the Repeatable Battery for the Assessment of Neuropsychological Status (DSST RBANS); scores averaged over the 2-, 4-, 6-, and 8-hour post-dose time points
  - Secondary endpoint: Change from baseline to the end of each double-blind treatment period on the British Columbia Cognitive Complaints Inventory (BC-CCI)
  - Safety and tolerability: Treatment-emergent adverse events (TEAEs)

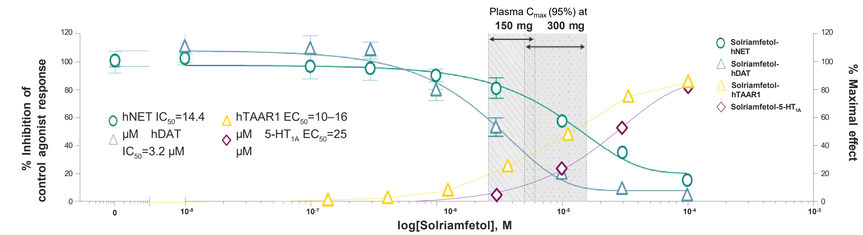
Figure 1. Intermittent Hypoxia and Sleep Fragmentation Protocols



Results

In Vitro

Figure 2. Solriamfetol Activates hTAAR1 and 5-HT_{1A} *In Vitro* at Clinically Relevant Plasma Concentrations



5-HT_{1A}, serotonin 1A receptor; DNRI, dopamine and norepinephrine reuptake inhibitor; C_{max}, maximum plasma concentration; EC_{50}, half maximal effective concentration; hDAT, human dopamine transporter; hNET, human norepinephrine transporter; hTAAR1, human trace amine-associated receptor 1; IC_{50}, half maximal inhibitory concentration; PI, prediction interval.

- Solriamfetol inhibits hDAT and hNET and has agonist activity at hTAAR1 and 5-HT^{1A} receptors
- No additional targets were identified for solriamfetol in a binding assay panel

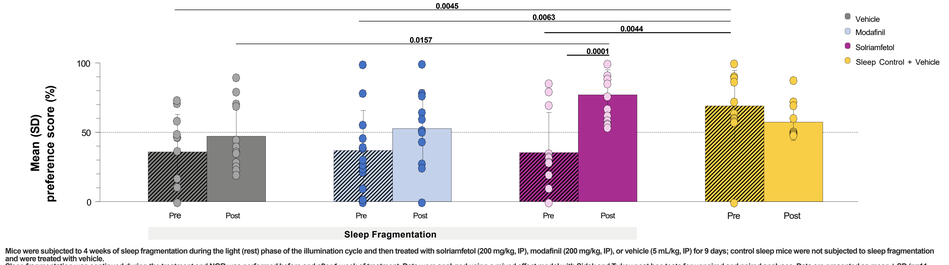
Murine Models

Figure 3. Solriamfetol Rescues Novel Object Recognition Performance Following Intermittent Hypoxia-Induced Memory Impairments

Mice were exposed to 16 weeks of intermittent hypoxia and treated with solriamfetol or modafinil for 9 days, during which intermittent hypoxia was continued; NOR was performed before and after 1 week of treatment. Preference scores in intermittent hypoxia groups before and after reatments with vehicle (5 mL/kg IP), modafinil (200 mg/kg IP), and solriamfetol (200 mg/kg IP) compared with room air control mice. Data were analyzed using a mixed effect model with Sidak and Tukey post hoc tests for unpaired and paired analyses. Data presented as mean ± SD (n=13–15/group).
IP, intraperitoneal; NOR, novel object recognition; SD, standard deviation.

- Solriamfetol significantly improved intermittent hypoxia-induced cognitive impairments as measured by the NOR test, whereas vehicle and modafinil failed to significantly improve performance

Figure 4. Solriamfetol Significantly Improves Novel Object Recognition Performance Following Chronic Sleep Fragmentation

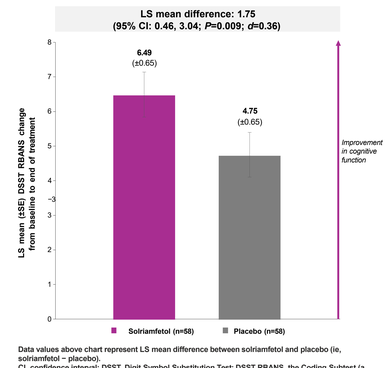


Mice were subjected to 4 weeks of sleep fragmentation during the light (rest) phase of the illumination cycle and then treated with solriamfetol (200 mg/kg, IP), modafinil (200 mg/kg, IP), or vehicle (5 mL/kg, IP) for 9 days; control sleep mice were not subjected to sleep fragmentation and were treated with vehicle.
Sleep fragmentation was continued during the treatment and NOR was performed before and after 1 week of treatment. Data were analyzed using a mixed effect model with Sidak and Tukey post hoc tests for unpaired and paired analyses. Data are presented as mean ± SD (n=11–14/experimental group).
IP, intraperitoneal; NOR, novel object recognition; SD, standard deviation.

- Solriamfetol significantly improved sleep fragmentation-induced cognitive impairments to levels greater than sleep-vehicle controls as measured by the NOR test; vehicle and modafinil failed to significantly improve performance
- Solriamfetol significantly reduced anxiety-like behavior in mice as measured by the EPMT following chronic intermittent hypoxia[14] and sleep fragmentation[13]; in both models, modafinil elicited an anxiogenic effect

Clinical Trial: SHARP

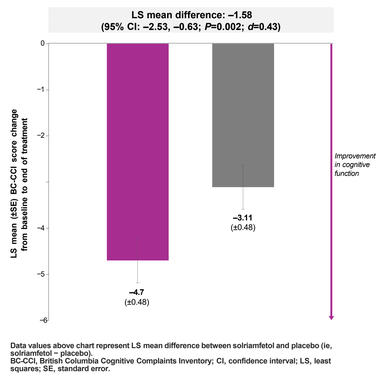
Figure 5. Objective Cognition, as Measured by DSST RBANS Scores, Significantly Improved After Solriamfetol Treatment Compared With Placebo



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.

- When evaluated at each 2-hour time point, DSST RBANS scores significantly improved with solriamfetol relative to placebo at 2 (P=0.033), 6 (P=0.004), and 8 (P=0.022) hours after dosing

Figure 6. Subjective Cognition, as Measured by BC-CCI Scores, Significantly 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.

- Overall, 16 of 59 (27%) patients in the safety population experienced any TEAE throughout the study; the most common TEAEs were nausea and anxiety, which is consistent with the known safety profile of solriamfetol
- All TEAEs were mild or moderate in severity; there were no deaths, serious TEAEs, or TEAEs that led to study discontinuation

Conclusions

- Solriamfetol is a DNRI with TAAR1 and 5-HT_{1A} agonist activity
- Solriamfetol rescued NOR performance (declarative memory) and ameliorated anxiety-like behavior in murine models of EDS in OSA, modeling improvements in behaviors representative of OSA and EDS; these effects were not seen with modafinil
- Solriamfetol improved objective and subjective cognition in the SHARP clinical trial in patients with impaired cognition associated with OSA and EDS
- Solriamfetol may serve as an effective treatment option for improving cognitive performance in patients with OSA and associated EDS
- The TAAR1 and 5-HT_{1A} agonist activity of solriamfetol may be relevant to other clinical conditions characterized by cognitive deficits

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