Neuroscience Education Institute Fall Congress
Nov 5-8, 2026
Colorado Springs, CO, USA

Solriamfetol for Excessive Daytime Sleepiness in Narcolepsy and OSA: Post-Hoc Multi-Dimensional Composite Endpoint Analysis of Phase 3 Trials

Ellen Wermter[1], Sam A. Kashani[2], Graham M. L. Eglit[3], Samantha Floam[3], Robert J. Thomas[4]
[1]Restorative Sleep Medicine, Charlottesville, VA, USA; [2]David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [3]Axsome Therapeutics, Inc., New York, NY, USA;
[4]Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Key Objective

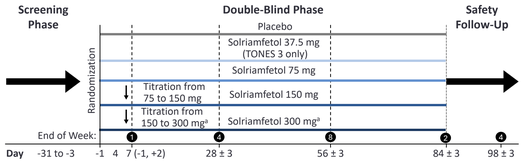
Evaluate clinically meaningful change across multiple and composite endpoints, comprising a range of objective and subjective outcomes from Phase 3 trials in narcolepsy and OSA

Introduction

- Excessive daytime sleepiness (EDS) is a symptom common to both narcolepsy and obstructive sleep apnea (OSA), associated with adverse consequences and burden severely impacting multiple aspects of life[1]
- Narcolepsy is a chronic neurologic disorder, caused by dysregulation of neurotransmitter pathways regulating both sleep and wake states.[2,3] OSA is characterized by repetitive upper airway obstruction leading to intermittent hypoxia, arousals, and sleep fragmentation[1,4]
- Solriamfetol (Sunosi®) is a dopamine-norepinephrine reuptake inhibitor, with agonist activity at the trace amine–associated receptor 1 (TAAR1) and serotonin 1A (5-hydroxytryptamine 1A [5-HT1A]) receptors[5-8]
- Solriamfetol is currently approved for the treatment of EDS in adults with narcolepsy (75-150 mg/day) or OSA (37.5-150 mg/day)[6-8]
- The safety and efficacy of solriamfetol has been previously evaluated for the treatment of EDS associated with narcolepsy and OSA in the Phase 3 TONES 2 (NCT02348593) and TONES 3 (NCT02348606) trials, respectively[9,10]
- In the current analysis, a composite assessment of clinically meaningful change on primary and secondary endpoints from the TONES 2 and 3 trials was undertaken to provide a more comprehensive understanding of the treatment effects of solriamfetol spanning objective and subjective outcomes
- Through demonstrating efficacy across a broad range of outcomes, a composite analysis of multiple assessment modalities may enable better treatment decisions based on overall clinical effect

Methods

Figure 1. TONES 2[9] and TONES 3[10] Study Design



TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.
[a]Participants randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on Days 1–3, with the full dose commencing on Day 4. The maximum recommended dose of solriamfetol in the US Prescribing Information is 150 mg once daily.[6]

- TONES 2 (n = 177) and TONES 3 (n = 356) were double-blind, randomized, placebo-controlled, 12-week trials (**Figure 1**) that evaluated both the safety and efficacy of solriamfetol for the treatment of EDS in narcolepsy or OSA, respectively[9,10]
- This analysis focuses on the approved solriamfetol doses of 75 mg and 150 mg approved for the treatment of EDS in adults with narcolepsy, in addition to the 37.5 mg dose approved for OSA
- In both trials, co-primary efficacy endpoints used the Epworth Sleepiness Scale (ESS) and Maintenance of Wakefulness Test (MWT). The key secondary endpoint used the Patient Global Impression of Change (PGI-C) scale, and secondary endpoints were assessed using the Clinical Global Impression of Change (CGI-C) scale and Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10)[9,10]
- Clinically meaningful change for multiple endpoints evaluated as part of this analysis were defined as follows[11]:
  - MWT ≥ 2-minute increase
  - ESS ≥ 2-point decrease[12]
  - PGI-C improvement (minimally, much or very much improved)[13]
  - CGI-C improvement (minimally, much, or very much improved)[13]
  - FOSQ-10 ≥ 1-point increase
- A responder in the composite analysis was defined as a participant who achieved ≥ 2-minute increase in MWT, ≥ 2-point decrease in ESS, and PGI-C improvement (minimally, much or very much improved)
- For both TONES 2 (narcolepsy) and TONES 3 (OSA), the percentage of participants achieving multiple endpoints (≥ 1 to ≥ 5), and a composite of primary and key secondary endpoints, were reported
- *P*-values were calculated using Chi Square tests without continuity correction for all thresholds and doses, except for solriamfetol 37.5 mg and 75 mg for ≥ 1 endpoint, as Fisher's exact test was used in these instances

Results

Baseline Characteristics in TONES 2 and TONES 3

Table 1. Baseline Characteristics (Safety Population)

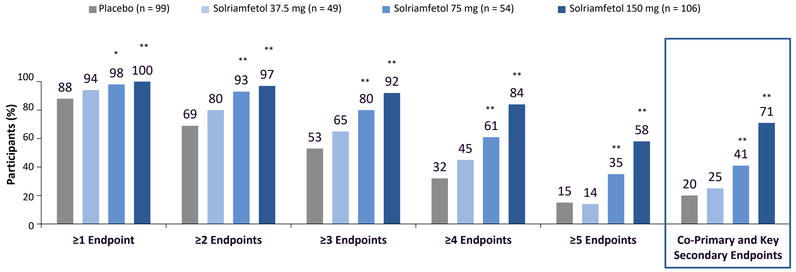
	TONES 2 (Narcolepsy)			TONES 3 (OSA)			
	Placebo (n = 59)	Solriamfetol 75 mg (n = 59)	Solriamfetol 150 mg (n = 59)	Placebo (n = 119)	Solriamfetol 37.5 mg (n = 58)	Solriamfetol 75 mg (n = 62)	Solriamfetol 150 mg (n = 117)
Age, years (SD)	36.0 (15.2)	36.5 (12.8)	38.1 (13.0)	54.1 (11.4)	57.1 (10.2)	54.4 (11.5)	52.7 (10.6)
Sex, male, n (%)	24 (40.7)	22 (37.3)	17 (28.8)	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)
Race, n (%)							
Asian	0	0	3 (5.1)	4 (3.4)	3 (5.2)	1 (1.6)	3 (2.6)
Black or African American	10 (16.9)	12 (20.3)	6 (10.2)	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)
White	47 (79.7)	46 (78.0)	48 (81.4)	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)
Other	2 (93.4)	1 (1.7)	2 (3.4)	2 (1.6)	0	1 (1.6)	3 (2.6)
BMI, kg/m^2 (SD)	29.1 (6.0)	27.9 (5.4)	27.9 (5.8)	33.1 (5.2)	34.1 (5.3)	33.4 (5.7)	33.3 (4.8)
MWT sleep latency, minutes (SD)	6.1 (5.6)	7.5 (5.4)	7.7 (5.6)	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)
ESS score, mean (SD)	17.3 (2.8)	17.3 (3.5)	16.9 (3.7)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.4)

- A total of 177 and 356 participants were included in the current analysis of the safety populations, from the TONES 2 and TONES 3 trials, respectively (**Table 1**)[9,10]
- Baseline demographic and clinical characteristics, including the MWT sleep latency and ESS score, were comparable across treatment groups within each trial

BMI, body mass index; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

Composite Endpoints in Participants With OSA

Figure 3. Proportion of Participants Achieving Multiple Endpoints or a Composite of the Co-Primary and Key Secondary Endpoints in TONES 3 (mITT Population)

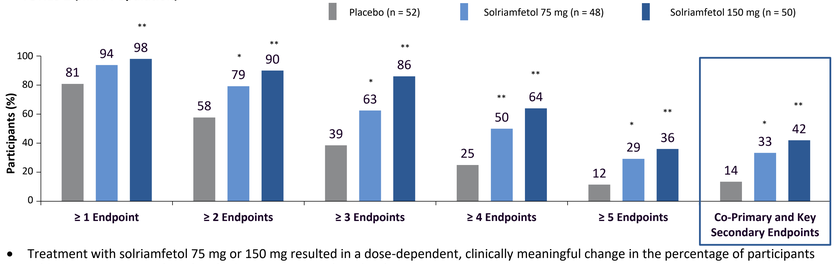


- In TONES 3, soriamfetol 75 mg or 150 mg resulted in a dose-dependent, concurrent clinically meaningful change in the percentage of participants achieving up to ≥ 5 combined endpoints, as compared to placebo. Statistical significance was not reached with soriamfetol 37.5 mg treatment across any of the endpoints evaluated within this multiple or composite analysis
- The percentage of participants with clinically meaningful change in the composite assessment of the co-primary and key secondary endpoints was 25% (absolute risk difference [95% CI]: 4% [–10-19%]; *P* = 0.551), 41% (absolute risk difference [95% CI]: 21% [5-36%]; *P* = 0.007) and 71% (absolute risk difference [95% CI]: 51% [39-62%]; *P* < 0.001) in the soriamfetol 37.5 mg, 75 mg, and 150 mg groups, respectively, compared with 20% in the placebo group (**Figure 3**)

*P≤0.05; **P≤0.01.
Co-primary and secondary endpoints were defined as MWT, ESS, and PGI-C.
mITT, modified intent-to-treat; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

Composite Endpoints in Participants With Narcolepsy

Figure 2. Proportion of Participants Achieving Multiple Endpoints or a Composite of the Co-Primary and Key Secondary Endpoints in TONES 2 (mITT Population)



- Treatment with soriamfetol 75 mg or 150 mg resulted in a dose-dependent, clinically meaningful change in the percentage of participants achieving up to ≥ 5 combined endpoints, as compared to placebo
- The percentage of participants with clinically meaningful change in the composite assessment of the co-primary and key secondary endpoints was 33% (absolute risk difference [95% CI]: 20% [4-36%]; *P* = 0.018) and 42% (absolute risk difference [95% CI]: 29% [12-45%]; *P* = 0.001) in the soriamfetol 75 mg and 150 mg groups, respectively, compared with 14% in the placebo group (**Figure 2**)

*P ≤ 0.05; **P ≤ 0.01.
Co-primary and secondary endpoints were defined as MWT, ESS, and PGI-C.
mITT, modified intent-to-treat; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

Pooled Safety in TONES 2 and TONES 3

Table 2. Dose-Dependent AEs in TONES 2 and TONES 3[6]

	Placebo (n = 226)	Solriamfetol 37.5 mg[a] (n = 58)	Solriamfetol 75 mg (n = 120)	Solriamfetol 150 mg (n = 218)
Headache[b]	8%	7%	9%	13%
Nausea[c]	5%	7%	5%	9%
Decreased appetite	1%	2%	7%	8%
Anxiety	1%	2%	3%	7%
Dry mouth	2%	2%	3%	4%
Diarrhea	2%	2%	4%	5%

- In the 12-week placebo-controlled clinical trials, 11 of the 396 participants (3%) who received soriamfetol discontinued because of an AE, compared to 1 of the 226 participants (< 1%) who received placebo (**Table 2**)
  - The AEs resulting in discontinuation that occurred in more than one soriamfetol-treated participant and at a higher rate than placebo were: anxiety, palpitations, and restlessness (n = 2/396; < 1% for each)

Note: Includes adverse reactions ≥ 2% in participants treated with soriamfetol and greater than placebo in TONES 2 or TONES 3.
AE, adverse event; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.
[a]In OSA only. [b,c]"Headache" includes headache, tension headache, and head discomfort. [c]"Nausea" includes nausea and vomiting.

Conclusions

- Solriamfetol treatment was associated with robust, dose-related efficacy, with most participants achieving efficacy in multiple endpoints, and significantly more participants achieving a composite of the primary and key secondary endpoints vs placebo for all doses except 37.5 mg
- Treatment with solriamfetol 75 mg or 150 mg was associated with clinically meaningful, multi-dimensional, and functional changes in objective and subjective measures of EDS, further illustrating efficacy in participants with narcolepsy and OSA

References

1. Sahni A, et al. *Nat Sci Sleep.* 2019;11:241-252. 2. Dauvilliers Y, et al. *Lancet.* 2007;369:499-511. 3. Latorre D, et al. *Semin Immunopathol.* 2022;44:611-623. 4. Pham L, et al. *Handb Clin Neurol.* 2022;189:105-136. 5. Gursahani H, et al. *Sleep.* 2022;45:A329. 6. Sunosi® (solriamfetol). Prescribing information. New York, NY: Axsome Therapeutics, Inc. 7. Sunosi® (solriamfetol). Product monograph including patient medical information. Malta: Axsome Malta Ltd.; 2022. 8. Sunosi® (solriamfetol) tablets. Summary of Product Characteristics. København S, Denmark: AtnaisPharma Netherlands B. V.; 2023. 9. Thorpy M, et al. *Ann Neurol.* 2019;85:359-370. 10. Schweitzer PK, et al. *Am J Respir Crit Care Med.* 2019;199:1421-1431. 11. Maski K. *J Clin Sleep Med.* 2021;17:1895-1945. 12. Patel S. *Am J Respir Crit Care Med.* 2018;197:961-963. 13. Weaver T, et al. *Sleep Breath.* 2021;25:1707-1715.

Acknowledgments

This study was funded and conducted by Axsome Therapeutics.
The authors would like to express their appreciation to the study participants and their families, as well as the investigators and site personnel. Under the direction of the authors, Sarah Edge, PhD, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, provided medical writing, editorial, and formatting support, which was funded by Axsome Therapeutics.

QR Code

Scan the QR code at the top of this poster or access **https://www.axsomemedicalaffairs.com/congress-presentations/NEI2026** to view or download a PDF of this poster or access additional information.

Disclosures

EW has served as a consultant, speaker, and/or on advisory boards for Avadel Pharmaceuticals, Axsome Therapeutics, Harmony Biosciences, and Jazz Pharmaceuticals. **SK** has served as a speaker for Avadel Pharmaceuticals, Axsome Therapeutics, Harmony Biosciences, and Jazz Pharmaceuticals. **GE** and **SF** are full-time employees of Axsome Therapeutics, Inc. **RT** has a patent and license to MyCardio, LLC for the ECG/PPG spectrogram, and has served as a consultant in general sleep medicine for GLG, Guidepoint, in addition to assisting in the development of the Respiratory self-similarity (detection of high loop gain sleep apnea) and Enhanced Expiratory Rebreathing Space (treatment of high loop gain sleep apnea), licensed to Sleepcare Asia.