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Solriamfetol and Maintenance of Wakefulness Outcomes in Patients With Narcolepsy and Obstructive Sleep Apnea

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Objective

- These post hoc analyses of the TONES 2 and TONES 3 study results characterized the effects of solriamfetol on the propensity of participants with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA) to maintain wakefulness as measured by various Maintenance of Wakefulness Test (MWT) thresholds related to improvement from baseline and mean sleep latency

Conclusions

- Solriamfetol was associated with clinically meaningful improvements (thresholds of ≥5, ≥10, ≥15, and ≥20 minutes) from baseline to week 12 in the MWT in participants with narcolepsy and OSA when compared with placebo
- A substantial portion of participants taking solriamfetol achieved MWT sleep latencies consistent with the normal range (20–40 min)
- Findings from these post hoc analyses suggest that solriamfetol leads to substantial improvements in the ability to stay awake in patients with narcolepsy or OSA

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Disclosures

M. Thorpy serves as a consultant to Axsome Therapeutics.
G.M.L. Eglit and **S. Floam** are employees of Axsome Therapeutics.
G. Parks is a former employee of Axsome Therapeutics.
L. Krahn serves as a consultant to Axsome Therapeutics.

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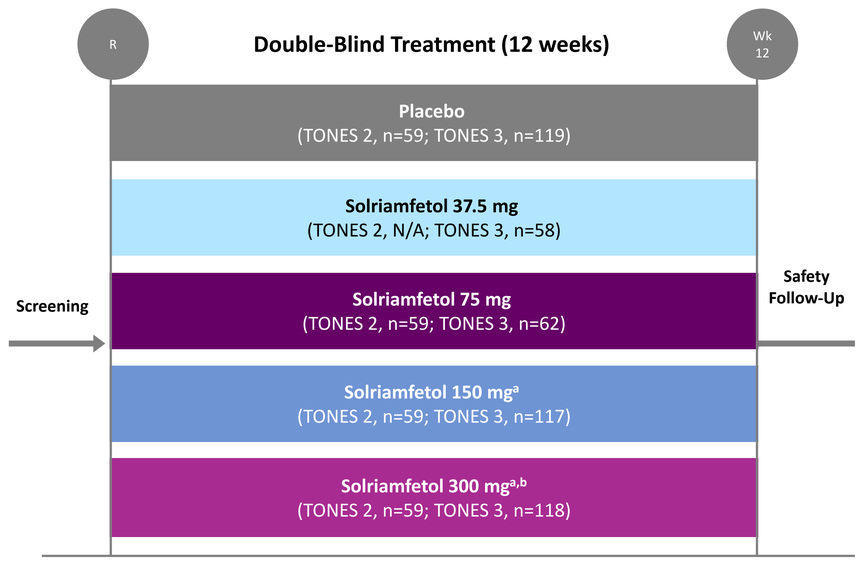
Introduction

- Patients with excessive daytime sleepiness (EDS) and narcolepsy or obstructive sleep apnea (OSA) struggle to maintain wakefulness[1-4]
- Solriamfetol (Sunosi®) is a dopamine-norepinephrine reuptake inhibitor with agonistic properties at the trace amine–associated receptor 1 (TAAR 1) and serotonin 1A (5-hydroxytryptamine 1A [5-HT1A]) receptors[5]; it is approved for use in adults in the United States, Canada, and select countries in Europe for the treatment of EDS associated with narcolepsy (75–150 mg/day) or OSA (37.5–150 mg/day)[6-8]
- The efficacy and safety of solriamfetol have been demonstrated in two 12-week phase 3 studies, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness (TONES) 2 (NCT02348593)[9] and TONES 3 (NCT02348606)[1]
- In both TONES 2 and TONES 3, solriamfetol showed robust therapeutic effects, including improvements from baseline compared with placebo in self-reported and objective sleepiness, as measured by the Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS), respectively[1,9]
  - Results from recent network meta-analyses suggest solriamfetol may provide more improvement in EDS as reflected by MWT and ESS scores than other wake-promoting agents such as modafinil, armodafinil, and pitolisant[10,11]
- The MWT is a diagnostic tool that provides objective measurement of patients' ability to stay awake for a given period of time[12]; higher latencies indicate a greater ability to stay awake, and positive change from baseline represents improvement in sleep latency
  - The MWT has high sensitivity and specificity across several sleep disorders, including narcolepsy and OSA; however, thresholds for determining clinically meaningful changes vary among clinicians[13]
  - There is no established cutoff for pathological MWT, but previous research showed that healthy participants had an average mean sleep latency of 35 minutes; the lower normal limit (2 standard deviations below mean) was 19 minutes[14]
  - Results from a systematic review commissioned by the American Academy of Sleep Medicine recommend a 2-minute improvement on the MWT as the minimum threshold for clinically meaningful improvement in sleep latency[15]

Methods & Study Design

- Participants were adult males and females 18–75 years of age who were diagnosed with narcolepsy (TONES 2) or OSA (TONES 3); detailed study design information has been previously published[1,9]
  - Key inclusion criteria included: having an ESS score ≥10, baseline 40-minute MWT mean sleep latency <25 minutes (narcolepsy) or <30 minutes (OSA), and total nightly sleep ≥6 hours; for patients with OSA, use of primary OSA therapy
  - Participants were randomly assigned to receive placebo or solriamfetol 37.5 mg (OSA only), 75 mg, 150 mg, or 300 mg once daily for 12 weeks (**Figure 1**)
  - Use of any over-the-counter or prescription medications that could affect the evaluation of EDS within a time period prior to the baseline visit corresponding to ≥5 half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study was not allowed
  - Coprimary endpoints of both studies were change from baseline to week 12 in mean sleep latency on the first 4 administrations of a 40-minute MWT and assessments of the ESS score
- These post hoc analyses evaluated the proportion of participants who achieved improvement from baseline on MWT thresholds of ≥5, ≥10, ≥15, and ≥20 minutes, and the proportion of participants who achieved mean sleep latencies of ≥20, ≥30, and 40 minutes at weeks 1, 4, and 12
- Comparisons between solriamfetol and placebo groups were evaluated among observed cases in the modified intent-to-treat population (defined as participants receiving ≥1 dose of study drug who had baseline evaluation and ≥1 MWT postbaseline evaluation of MWT or ESS) using Fisher's exact test

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



Note: n numbers indicate the safety population, consisting of all participants who received ≥1 dose of study medication.
R, randomization; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.
[a]Participants assigned to the 150- and 300-mg doses received 75 and 150 mg, respectively, for the first 3 days and the full dose thereafter.
[b]Not an approved dose.

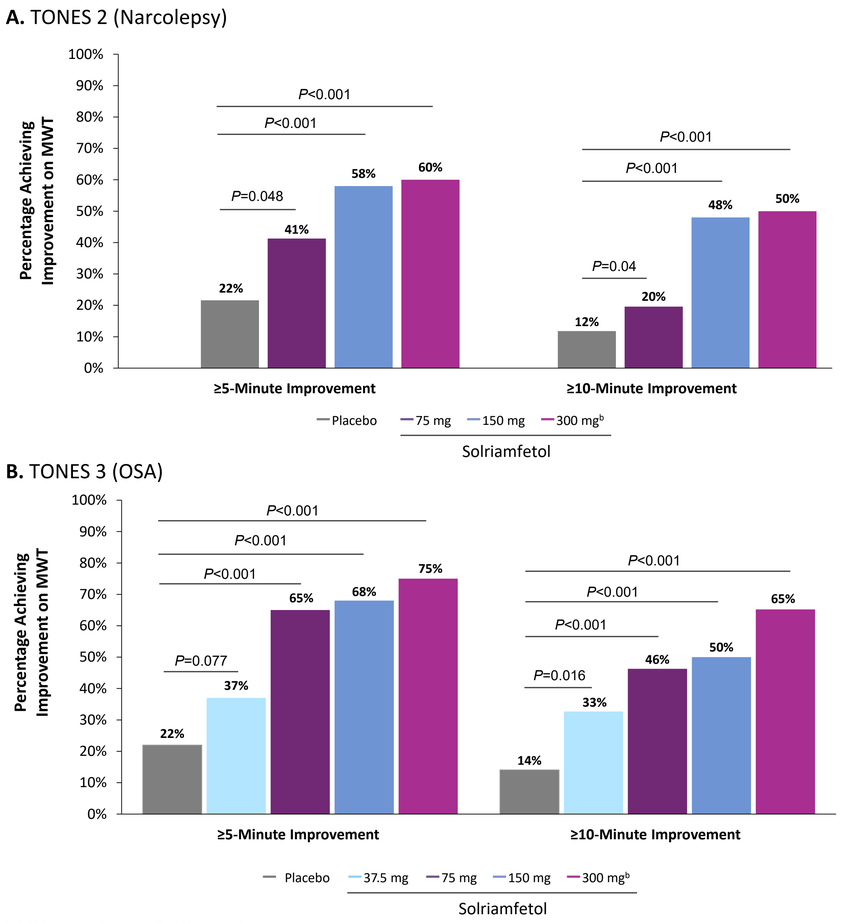
Key Findings

Patient Population

- Baseline demographics and disease characteristics have been previously reported[1,9]
- Mean MWT sleep latencies at baseline across placebo and solriamfetol groups ranged from 6.1 to 8.7 minutes in participants with narcolepsy and 12.0 to 13.6 minutes in those with OSA

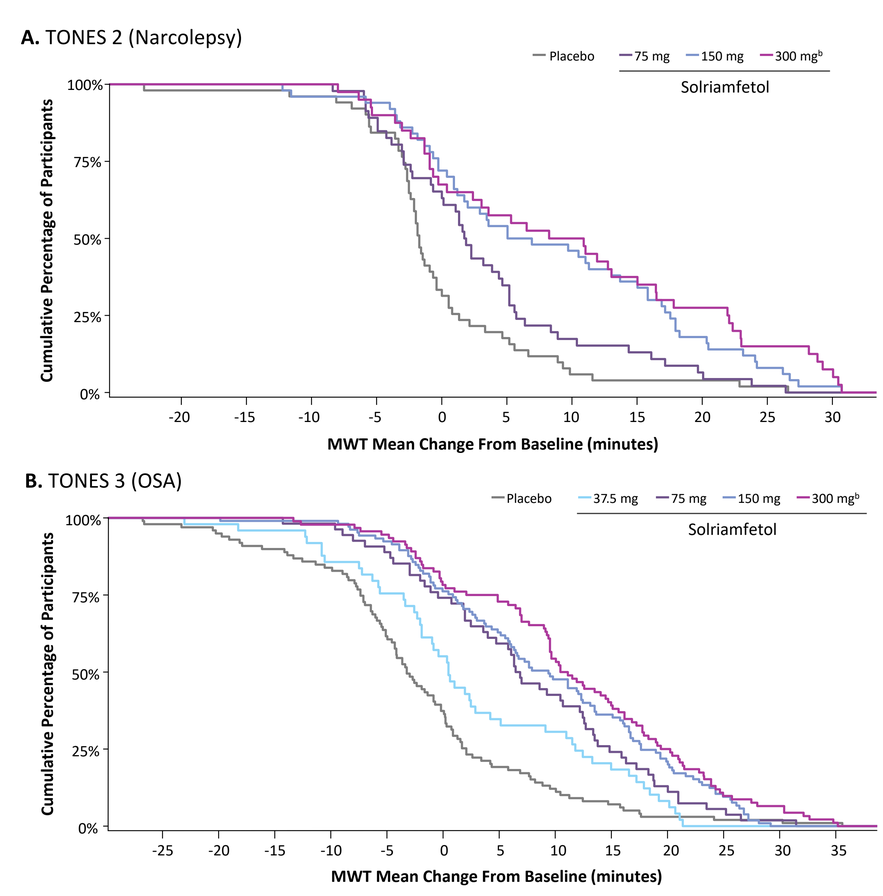
Improvements From Baseline in MWT

Figure 2. Participants With (A) Narcolepsy[a] and (B) OSA Who Achieved Improvement on the MWT From Baseline to Week 12



MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnea.
[a]In TONES 2 , the percentage of participants with narcolepsy with cataplexy was 49% and 51% in the placebo and solriamfetol treatment groups, respectively.
[b]Not an approved dose.

Figure 3. Cumulative Proportions of Participants With (A) Narcolepsy[a] and (B) OSA With Mean MWT Changes From Baseline to Week 12 by Treatment Group

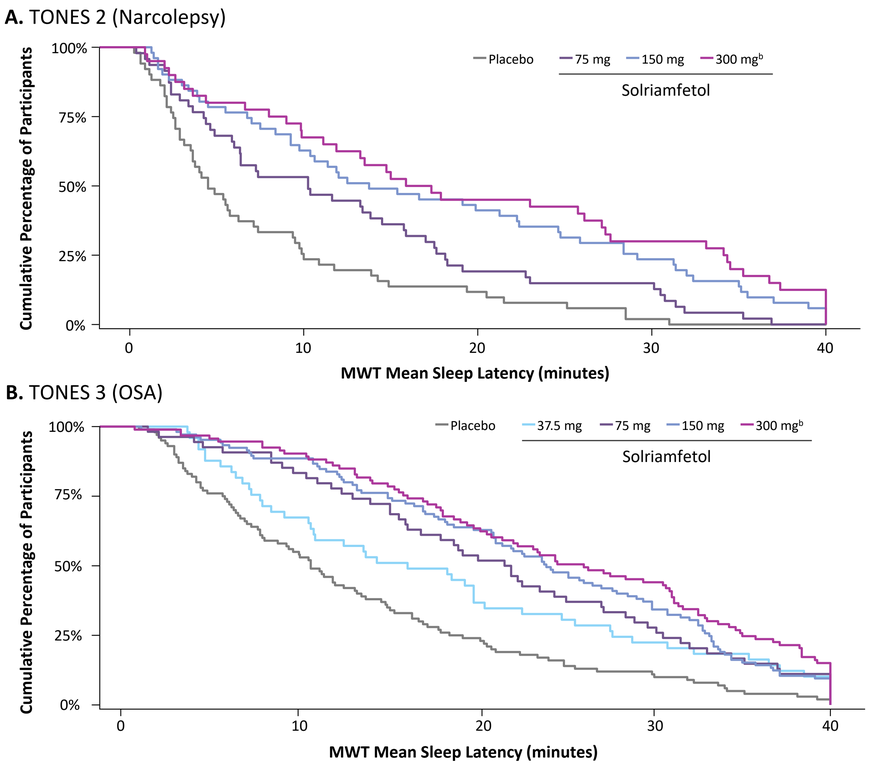


MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnea.
[a]In TONES 2 , the percentage of participants with narcolepsy with cataplexy was 49% and 51% in the placebo and solriamfetol treatment groups, respectively.
[b]Not an approved dose.

- Participants with narcolepsy and OSA who were randomized to solriamfetol showed greater improvements from baseline in MWT at each time threshold (≥5, ≥10, ≥15, and ≥20 minutes) compared with placebo recipients; results for ≥5- and ≥10-minute improvements are shown in **Figure 2**
  - A significantly greater proportion of participants randomized to solriamfetol 75 mg (OSA only; $P \leq 0.03$), 150 mg (all; $P \leq 0.03$), and 300 mg (all; $P \leq 0.002$) achieved ≥15- and ≥20-minute improvement from baseline in MWT compared with placebo
- Cumulative proportions of participants with MWT mean changes from baseline are presented in **Figure 3**

MWT Sleep Latency

Figure 4. Cumulative Proportions of Participants With (A) Narcolepsy[a] and (B) OSA With MWT Sleep Latency up to 40 Minutes at Week 12 by Treatment Group



MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnea.
[a]In TONES 2 , the percentage of participants with narcolepsy with cataplexy was 49% and 51% in the placebo and solriamfetol treatment groups, respectively.
[b]Not an approved dose.

- Cumulative proportions of participants who achieved MWT mean sleep latency up to 40 minutes are shown in **Figure 4**
- Overall, a greater proportion of participants with narcolepsy and OSA achieved sleep latencies of ≥20, ≥30, and 40 minutes with solriamfetol than with placebo (**Table 1**)

Table 1. Proportions of Participants Who Achieved ≥20-, ≥30-, and 40-Minute Mean Sleep Latency on the MWT at Week 12

Treatment	TONES 2 (Narcolepsy[a])			TONES 3 (OSA)		
	≥20-Minute	≥30-Minute	40-Minute	≥20-Minute	≥30-Minute	40-Minute
Solriamfetol dose						
37.5 mg	NA	NA	NA	37%	22%	10%
75 mg	19%	15%	0%	54%	28%	11%
150 mg	41%	24%	6%	63%	34%	10%
300 mg[b]	45%	30%	13%	63%	44%	15%
Placebo	12%	2%	0%	24%	11%	2%

MWT, Maintenance of Wakefulness Test; NA, not applicable; OSA, obstructive sleep apnea.
[a]In TONES 2, the percentage of participants with narcolepsy with cataplexy was 49% and 51% in the placebo and solriamfetol treatment groups, respectively.
[b]Not an approved dose.