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Solriamfetol for Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea: Effect Sizes and Numbers Needed to Treat or Harm

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Introduction

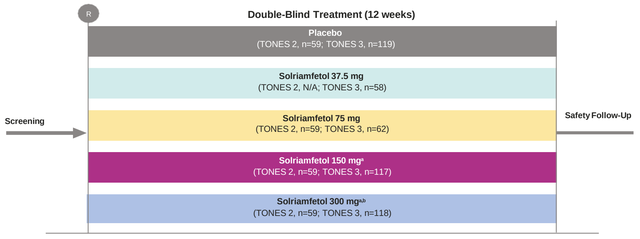
- Excessive daytime sleepiness (EDS) is common in patients with narcolepsy and obstructive sleep apnea (OSA) and can lead to impaired cognitive functioning, poor work productivity, and reduced quality of life[1-6]
- Solriamfetol (Sunosi®), a dopamine and norepinephrine reuptake inhibitor, is approved for use in adults in the United States and European Union for the treatment of EDS associated with narcolepsy (75–150 mg/day) or OSA (37.5–150 mg/day)[7,8]
  - Preclinical data indicate that solriamfetol activates trace amine-associated receptor 1 (TAAR1), a potential target for improving cognitive functions[9,10]
- The efficacy and safety of solriamfetol have been established in two phase 3 studies, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness (TONES) 2 and TONES 3[11,12]; efficacy was demonstrated based on (ESS)[13] scores, Maintenance of Wakefulness Test (MWT)[14] mean sleep latency, and Patient and Clinical Global Impression of Change (PGIc and CGIc)[15]
- Effect size, number needed to treat (NNT), and number needed to harm (NNH) are statistical representations of efficacy and tolerability, and as such may be helpful in guiding clinicians' treatment decisions[16]

Objective

- This post hoc analysis characterized efficacy and tolerability of solriamfetol based on effect sizes, NNT, and NNH using data from TONES 2 and TONES 3

Methods

Figure 1. TONES 2 and TONES 3 Study Design[11,12]



TONES 2 (NCT02348593), TONES 3 (NCT02348606). Participares were adult males and females 18–75 years of age and diagnosed with narcolepsy or OSA. Key inclusion criteria were EDS (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, primary OSA therapy (current or prior use of PAP, mandibular advancement device, or surgical intervention). Key exclusion criteria were usual bedtime later than 1:00 AM, nighttime employment or variable shift work, or diagnosis of any disorder (other than narcolepsy or OSA) associated with EDS. Note: n values indicate safety population.
[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.
EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; N/A, not applicable; OSA, obstructive sleep apnea; PAP, positive airway pressure; R, randomization; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

- Effect sizes compared with placebo (Cohen's *d*) were determined for ESS scores and MWT mean sleep latency, based on changes from baseline to week 12
  - Cohen's *d* effect sizes: small (*d*=0.2), medium (*d*=0.5), and large (*d*=0.8)[17]
- NNT (<10 is favorable[16]) was determined for the percentage of participants with scores/changes in scores that met clinically meaningful response thresholds at week 12:
  - For ESS: ESS ≤10, ≥25% decrease from baseline, and 3-point decrease from baseline
  - For MWT: Achieving a mean sleep latency ≥20 minutes and 2-minute increase from baseline
  - For PGIc and CGIc: Improvement, defined as responses of "minimally," "much," or "very much" improved
- NNH (≥10 is favorable[16]) was determined for treatment- emergent adverse events (TEAEs) that were reported in ≥5% of solriamfetol-treated participants and greater than placebo

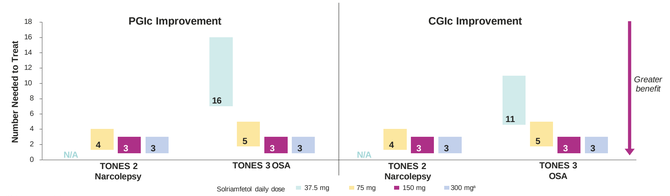
Results

Table 1. In TONES 2 and 3, Favorable Effect Sizes Were Seen for Solriamfetol Compared With Placebo

Solriamfetol dose	ESS		MWT	
	TONES 2 (Narcolepsy)	TONES 3 (OSA)	TONES 2 (Narcolepsy)	TONES 3 (OSA)
37.5 mg/day	N/A	0.42	N/A	0.46
75 mg/day	0.47	0.37	0.29	0.89
150 mg/day	0.80	0.99	0.82	1.08
300 mg/day[a]	1.03	1.04	1.13	1.28

Effect sizes (Cohen's *d*) based on mean changes from baseline. [a]Not an approved dose.
ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; N/A, not applicable; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

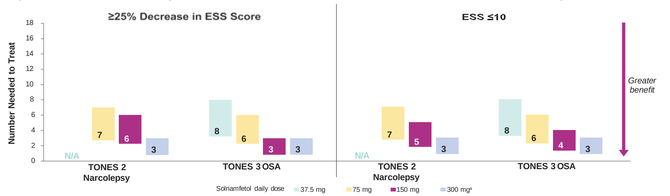
Figure 2. NNT for Categorical Improvement in PGIc and CGIc for Solriamfetol Compared With Placebo



[a]Not an approved dose.
CGIc, Clinical Global Impression of Change; N/A, not applicable; NNT, number needed to treat; OSA, obstructive sleep apnea; PGIc, Patient Global Impression of Change; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

- Compared with placebo, with solriamfetol 150 mg/day, 3 participants with narcolepsy or OSA would need to be treated for 1 additional participant to achieve PGIc or CGIc response

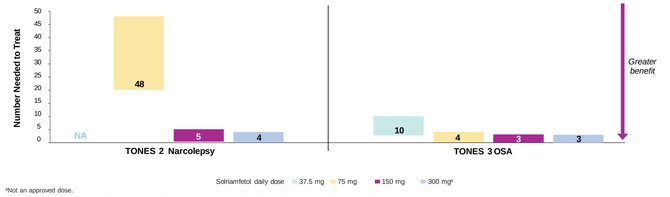
Figure 3. NNT for Achieving ≥25% Decrease in ESS Score or ESS ≤10 for Solriamfetol Compared With Placebo



[a]Not an approved dose.
ESS, Epworth Sleepiness Scale; N/A, not applicable; NNT, number needed to treat; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

- Compared with placebo, with solriamfetol 150 mg/day:
  - 6 participants with narcolepsy and 3 participants with OSA would need to be treated for 1 additional participant to achieve ≥25% decrease in ESS score
  - 5 participants with narcolepsy and 4 participants with OSA would need to be treated for 1 additional participant to achieve ESS scores in the normal range

Figure 4. NNT for Achieving MWT of ≥20 Minutes for Solriamfetol Compared With Placebo in Participants With OSA



[a]Not an approved dose.
MWT, Maintenance of Wakefulness Test; NNT, number needed to treat; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

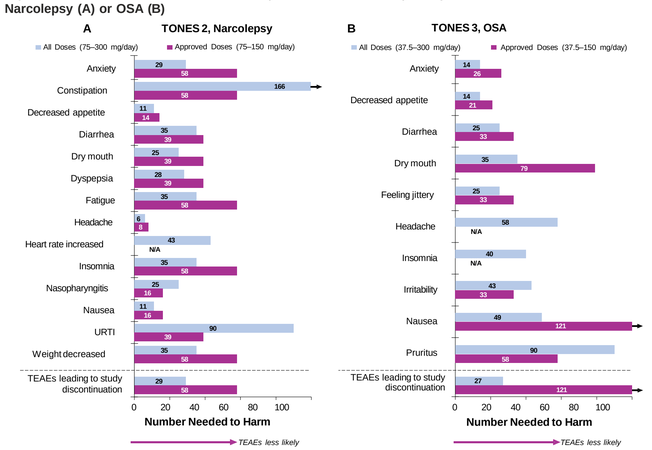
- Compared with placebo, with solriamfetol 150 mg/day, 3 participants with OSA would need to be treated for 1 additional participant to achieve MWT ≥20 minutes

Table 2. Summary of Effect Sizes and NNT With Solriamfetol in TONES 2 and TONES 3

Study Solriamfetol dose	ESS				MWT			PGIc	CGIc
	Cohen's *d*[b]	NNT (ESS ≤10)	NNT (↓ ≥25%)	NNT (↓3 points)	Cohen's *d*[b]	NNT (≥20 min)	NNT (↑2 min)	NNT	NNT
TONES 2 (Narcolepsy)									
75 mg/day	0.47	7	7	6	0.29	48	5	4	4
150 mg/day	0.80	5	6	4	0.82	5	3	3	3
300 mg/day[a]	1.03	3	3	3	1.13	4	3	3	3
TONES 3 (OSA)									
37.5 mg/day	0.42	8	8	7	0.46	10	7	16	11
75 mg/day	0.37	6	6	7	0.89	4	3	5	5
150 mg/day	0.99	4	3	3	1.08	3	3	3	3
300 mg/day[a]	1.04	3	3	3	1.28	3	3	3	3

[a]Based on mean change from baseline. [b]Not an approved dose.
ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness on mean Test; N/A, not applicable/data not available; NNT, number needed to treat; OSA, obstructive sleep apnea; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness.

Figure 5. NNH for TEAEs[a] for Solriamfetol (Pooled Across Doses) Compared With Placebo in Patients With Narcolepsy (A) or OSA (B)



[a]TEAEs reported by ≥5% in any treatment group.
AEs, adverse events; N/A, not applicable; NNH, number needed to harm; OSA, obstructive sleep apnea; TEAE, treatment-emergent adverse event; TONES, Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness; URTI, upper respiratory tract infection.

- Across pooled doses with and without 300 mg of solriamfetol, only 1 TEAE had a NNH <10 (headache, in participants with narcolepsy)

Conclusions

- In TONES 2 and TONES 3, large effect sizes were observed for improvement in ESS and MWT with higher solriamfetol doses
- Across all outcomes, NNT with the 150 mg/day dose of solriamfetol ranged from 3 to 6 in patients with narcolepsy (TONES 2) and from 3 to 4 in patients with OSA (TONES 3)
- NNH pooled across all doses and across approved doses of solriamfetol for common TEAEs were >10, except for headache in TONES 2
- This post hoc analysis demonstrates favorable effect sizes and NNT and NNH values for solriamfetol in the treatment of EDS associated with narcolepsy and OSA

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