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SCIENTIFIC INVESTIGATIONS

Clinically relevant effects of solriamfetol on excessive daytime sleepiness: a posthoc analysis of the magnitude of change in clinical trials in adults with narcolepsy or obstructive sleep apnea

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Study Objectives: To evaluate the clinical relevance of solriamfetol in treating excessive daytime sleepiness in participants with narcolepsy or obstructive sleep apnea (OSA).

Methods: This posthoc analysis includes data from two 12-week, randomized phase 3 studies in participants with narcolepsy or OSA treated with once-daily placebo or solriamfetol 37.5 mg (OSA only), 75 mg, 150 mg, or 300 mg. Excessive daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) at baseline and at week 12. Cumulative distribution function plots were generated using a last-observation-carried-forward approach to determine the percentage of participants who achieved ESS scores ≤ 10, within the normal range, and the percentage who achieved a reduction (improvement) in ESS ≥ 25% relative to baseline. Safety was also assessed.

Results: In narcolepsy (n = 231), 30.5%–49.2% of participants treated with solriamfetol (across doses) reported ESS scores ≤ 10 and 44.1%–62.7% achieved a ≥ 25% decrease from baseline in ESS scores at week 12, compared with 15.5% and 27.6%, respectively, of placebo recipients. In OSA (n = 459), 51.8%–73.0% of participants treated with solriamfetol (across doses) reported ESS scores ≤ 10 and 50.0%–81.9% achieved a ≥ 25% decrease from baseline in ESS scores at week 12, compared with 37.7% and 36.8%, respectively, of placebo recipients. Results were generally dose-dependent, with more responders at higher solriamfetol doses. Common treatment-emergent adverse events (≥ 5% of solriamfetol recipients in either study) were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety.

Conclusions: A greater percentage of participants treated with solriamfetol achieved normal ESS scores (≤ 10) or clinically meaningful improvements on the ESS compared with those receiving placebo. The safety profile was similar between participants with narcolepsy and those with OSA.

Clinical Trial Registrations: Registry: ClinicalTrials.gov. Names: TONES 2 and TONES 3. URLs: https://www.clinicaltrials.gov/ct2/show/NCT02348593 and https://www.clinicaltrials.gov/ct2/show/NCT02348606. Identifiers: NCT02348593, NCT02348606. Registry: European Union Drug Regulating Authorities Clinical Trials. Names: TONES 2 and TONES 3. URL: https://www.eudract.ema.europa.eu. Identifiers: EudraCT 2014-005487-15, EudraCT 2014-005514-31.

Keywords: JZP-110, Sunosi, sleepiness, hypersomnolence, narcolepsy, OSA, self-report, clinical relevance, responder, normalization

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Solriamfetol has shown robust wake-promoting effects in previous phase 3 clinical trials in participants with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). This posthoc analysis aimed to evaluate the clinical relevance of these effects.

Study Impact: A greater percentage of participants receiving solriamfetol vs placebo reported Epworth Sleepiness Scale scores within the normal range (≤ 10) and had reductions (improvements) of ≥ 25% from baseline, an established clinically meaningful change on the Epworth Sleepiness Scale. The safety profile of solriamfetol was similar in participants with narcolepsy and participants with OSA.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a major symptom of narcolepsy (both type 1 and type 2) and obstructive sleep apnea (OSA), affecting all patients with narcolepsy and up to 65% of patients with untreated OSA.[1–6] EDS has a profound impact on patients, including impaired daily functioning, reduced health-related quality of life, and increased risk of workplace and driving accidents.[7–10] For patients with OSA, EDS can persist despite the use of primary OSA therapy and is reported by an estimated 9%–22% of patients treated with continuous positive airway pressure therapy.[5,11] Because of the substantial impact of EDS on patients with narcolepsy or OSA and the relatively high prevalence of EDS among patients with narcolepsy or OSA, symptomatic pharmacologic treatment for EDS is warranted.

Several pharmacologic therapies are available for the treatment of EDS in patients with narcolepsy or OSA, including wake-promoting agents, stimulants, and sodium oxybate (narcolepsy only).[12–17] Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, has been approved in the United

States and the European Union to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA.[18,19] The approved dose range of solriamfetol is 75–150 mg once daily for patients with narcolepsy and 37.5–150 mg once daily for patients with OSA.[18] In previous 12-week, randomized, double-blind, placebo-controlled phase 3 clinical trials, solriamfetol showed robust wake-promoting effects in participants with narcolepsy or OSA.[20,21] Specifically, solriamfetol significantly improved self-reported and objective measures of sleepiness, as assessed by mean changes on the Epworth Sleepiness Scale (ESS) and the Maintenance of Wakefulness Test (MWT), respectively, relative to placebo. Although the efficacy of solriamfetol in treating EDS has been established, the clinical relevance of these effects had not been further characterized in terms of how many participants have experienced clinically meaningful changes.

The ESS is a validated, patient-reported questionnaire that assesses the propensity to fall asleep in real-world situations.[22] Scores ≤ 10 are considered within the normal range, whereas scores > 10 indicate EDS; therefore, evaluating the percentage of patients who achieve scores ≤ 10 provides a measure of the percentage of patients with remitted symptoms.[22,23] In addition to achievement of an ESS score ≤ 10, a clinically meaningful percent reduction (improvement) in ESS scores relative to baseline can also be assessed. A reduction in ESS score ≥ 25% from baseline has been identified as a clinically relevant threshold to classify patients who respond to solriamfetol treatment.[24,25]

The aim of the current posthoc analysis was to further examine the clinical relevance of changes in ESS scores in participants treated with solriamfetol by evaluating the percentage of participants who exhibited clinically meaningful responses on the ESS in two 12-week, phase 3 solriamfetol studies. Specifically, the percentage of participants who reported ESS scores within the normal range (≤ 10) and the percentage of participants who achieved ≥ 25% improvement from baseline in ESS score were evaluated.

METHODS

Study design

This posthoc analysis includes data from two 12-week, randomized, placebo-controlled, parallel-group, phase 3 clinical trials that evaluated the efficacy and safety of solriamfetol in the treatment of EDS in adults with narcolepsy[20] or OSA.[21] Both studies were approved by institutional review boards or ethics committees at each institution and were performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. Full descriptions of the studies' design and results have been reported previously[20,21] and are briefly summarized herein.

Participants

Eligible participants were adults (aged 18–75 years) diagnosed with narcolepsy (type 1 or type 2) or OSA with a baseline ESS score ≥ 10. Additional key inclusion criteria included a baseline mean sleep latency < 25 minutes (narcolepsy) or < 30 minutes (OSA) on the MWT, a usual nightly total sleep time ≥ 6 hours, and, for participants with OSA, at least minimal stable use of a primary OSA therapy. Key exclusion criteria included a usual bedtime later than 1:00 AM, an occupation requiring nighttime or variable shift work, or any other clinically relevant medical, behavioral, or psychiatric disorder associated with EDS.

Treatment

Participants with narcolepsy were randomly assigned (1:1:1:1) to 12 weeks of treatment with placebo or solriamfetol 75 mg, 150 mg, or 300 mg once daily. Participants with OSA were randomly assigned (2:1:1:2:2) to 12 weeks of treatment with placebo or solriamfetol 37.5 mg, 75 mg, 150 mg, or 300 mg once daily.

EDS and safety assessments

For the purpose of the current analyses, outcomes were based on EDS, as evaluated with the ESS at baseline and at week 12. The safety and tolerability of solriamfetol were evaluated across the study durations, and treatment-emergent adverse events (TEAEs) were summarized.

Statistical analysis

Baseline characteristics were summarized for the modified intent-to-treat populations, defined as participants who received ≥ 1 dose of the study drug and had a baseline and ≥ 1 postbaseline ESS or MWT assessment. ESS analyses were based on the modified intent-to-treat populations using a last-observation-carried-forward approach. Cumulative distribution function plots were generated for ESS score and percent change from baseline in ESS score at week 12 to determine the percentage of participants who achieved an ESS score ≤ 10 (ie, within the normal range)[22,23] and the percentage of participants who achieved a ≥ 25% reduction (improvement) in ESS score relative to baseline at week 12, a clinically meaningful change.[24] These data were used to determine a number needed to treat (NNT) for each outcome. Because this was a posthoc analysis, no further statistical analyses were performed to compare treatments or the narcolepsy and OSA populations. TEAEs were summarized descriptively for the safety populations, defined as participants who received ≥ 1 dose of the study drug.

RESULTS

Participant population

A total of 364 participants with narcolepsy and 984 participants with OSA were screened for eligibility. Of these, 239 were enrolled in the narcolepsy study and 476 entered the OSA study; 236 (98.7%) participants with narcolepsy and 474 (99.6%) participants with OSA were included in the safety populations, and 231 (96.7%) participants with narcolepsy and 459 (96.4%) participants with OSA were included in the modified intent-to-treat populations. A total of 195 (81.6%) participants with narcolepsy and 404 (84.9%) participants with OSA completed the respective studies, with the most frequently reported reasons for discontinuation being adverse events, withdrawal of consent, and, for participants with narcolepsy, lack of efficacy.[20,21]

Table 1—Baseline characteristics (mITT populations).

Variable	Narcolepsy		OSA	
	Placebo (n = 58)	Solriamfetol, All Doses (n = 173)	Placebo (n = 114)	Solriamfetol, All Doses (n = 345)
Age, y, mean (SD)	36.2 (15.2)	36.2 (12.4)	54.0 (11.5)	53.8 (10.8)
Male (%)	41.4	32.9	64.0	62.0
BMI, kg/m^2, mean (SD)	29.3 (5.8)	28.0 (5.8)	33.1 (5.3)	33.3 (5.3)
ESS score, mean (SD)	17.3 (2.9)	17.2 (3.3)	15.6 (3.3)	15.1 (3.3)

BMI = body mass index, ESS = Epworth Sleepiness Scale, mITT = modified intent-to-treat, OSA = obstructive sleep apnea, SD = standard deviation.

Participants with narcolepsy were predominantly female and had a younger mean age and a lower mean body mass index compared with participants with OSA (**Table 1**). At baseline, mean ESS scores were numerically higher in the narcolepsy population than in the OSA population (**Table 1**).

ESS

In participants with narcolepsy, mean (standard deviation) scores at week 12 were 13.8 (5.6), 11.5 (5.5), and 11.1 (5.3) for the solriamfetol 75 mg, 150 mg, and 300 mg dose groups, respectively, compared with 15.7 (4.6) for placebo. The range of ESS scores at week 12 was 3–23 in the solriamfetol 75 mg group, 2–23 in the 150 mg group, 2–22 in the 300 mg group, and 6–23 in the placebo group. At week 12, 30.5% (95% confidence interval [CI], 19.2%–43.9%), 40.0% (95% CI, 27.0%–54.1%), and 49.2% (95% CI, 35.9%–62.5%) of participants randomly assigned to receive solriamfetol 75 mg, 150 mg, and 300 mg, respectively, reported an ESS score ≤ 10, compared with 15.5% (95% CI, 7.3%–27.4%) of participants assigned to placebo (**Figure 1A**), for NNTs of 7, 5, and 3, respectively. In addition, 44.1% (95% CI, 31.2%–57.6%), 47.3% (95% CI, 33.7%–61.2%), and 62.7% (95% CI, 49.1%–75.0%) of participants receiving solriamfetol 75 mg, 150 mg, and 300 mg, respectively, had ≥ 25% reduction from baseline in their ESS score at week 12, compared with 27.6% (95% CI, 16.7%–40.9%) of placebo recipients (**Figure 1B**), for NNTs of 7, 6, and 3, respectively. Results were generally dose-dependent, such that the percentage of participants who achieved normal responses increased with larger solriamfetol doses.

In participants with OSA, mean (standard deviation) scores at week 12 were 9.7 (5.3), 10.0 (5.2), 7.5 (4.7), and 7.1 (4.8) for the solriamfetol 37.5 mg, 75 mg, 150 mg, and 300 mg dose groups, respectively, compared with 12.2 (4.5) for placebo. The range of ESS scores at week 12 was 0–22 in the solriamfetol 37.5 mg group, 1–21 in the 75 mg group, 0–18 in the 150 mg group, 0–20 in the 300 mg group, and 1–23 in the placebo group. At week 12, 51.8% (95% CI, 38.0%–65.3%), 55.2% (95% CI, 41.5%–68.3%), 70.7% (95% CI, 61.5%–78.8%), and 73.0% (95% CI, 64.0%–80.9%) of participants randomly assigned to receive solriamfetol 37.5 mg, 75 mg, 150 mg, and 300 mg, respectively, reported an ESS score ≤ 10 at week 12, compared with 37.7% (95% CI, 28.8%–47.3%) of placebo recipients (**Figure 2A**), for NNTs of 8, 6, 4, and 3, respectively. In addition, 50.0% (95% CI, 36.3%–63.7%), 55.2% (95% CI, 41.5%–68.3%), 81.9% (95% CI, 73.7%–88.4%), and 75.7% (95% CI, 66.8%–83.2%) of participants receiving solriamfetol 37.5 mg, 75 mg, 150 mg, and 300 mg, respectively, had ≥ 25% reduction from baseline in their ESS score at week 12, compared with 36.8% (95% CI, 28.0%–46.4%) in the placebo group (**Figure 2B**), for NNTs of 8, 6, 3, and 3, respectively. Results were generally dose-dependent, such that the higher doses (150 mg and 300 mg) yielded a higher percentage of responders than the lower doses (37.5 mg and 75 mg).

Safety

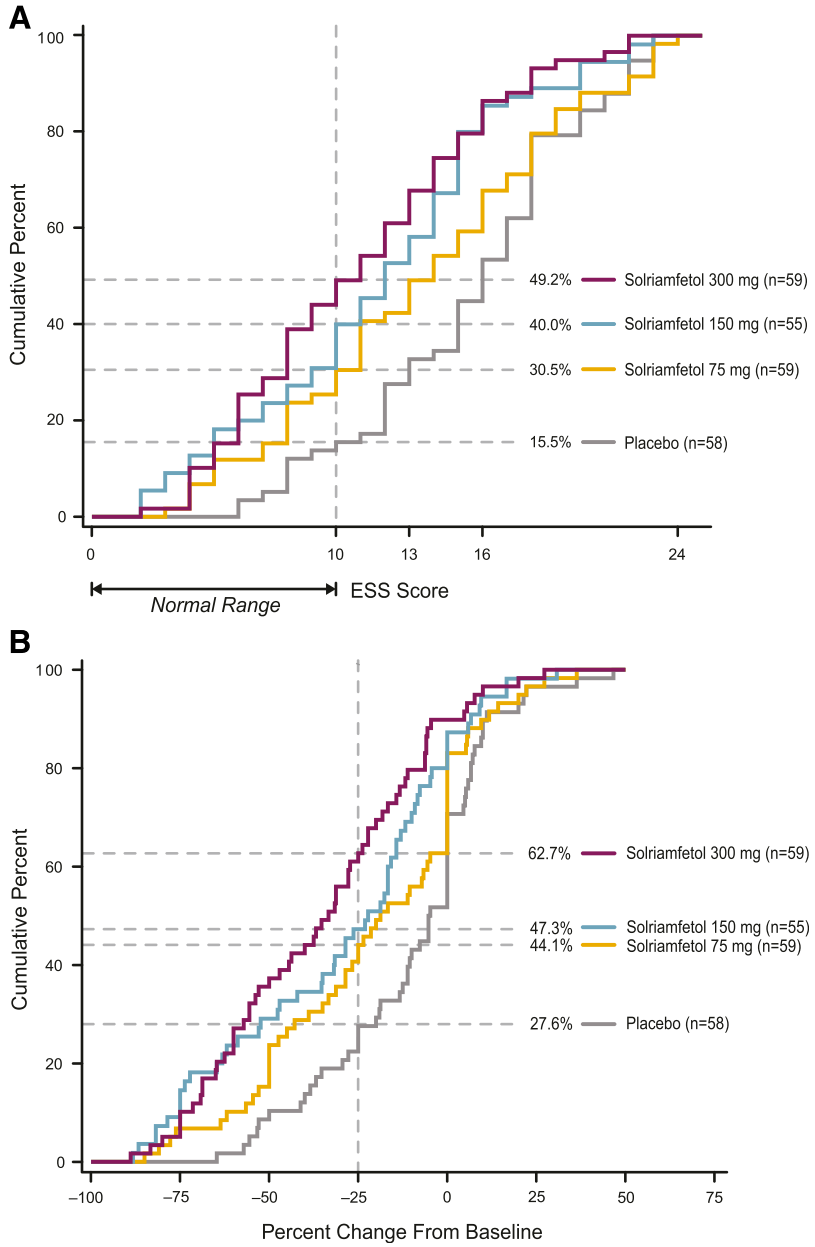
The most frequently reported TEAEs (reported in ≥ 5% of participants treated with solriamfetol [all doses] for either indication) were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety. The incidence of these TEAEs was generally higher with higher doses of solriamfetol (150 mg and 300 mg). The majority of TEAEs were mild or moderate in severity, and no serious TEAEs were considered related to the study drug, as assessed by the investigator. No deaths occurred in either study. In general, the safety profiles were similar between the narcolepsy and OSA populations (**Table 2**).

DISCUSSION

Consistent with the previous publication of the primary efficacy analyses of these studies in adult participants with narcolepsy[20] or OSA,[21] the current posthoc analyses provide further evidence that solriamfetol results in robust improvements in EDS in these populations and expand on the previous findings of significant mean improvements from baseline compared with placebo by showing that these improvements are of a magnitude that is clinically meaningful for a substantial number of participants. Specifically, a greater percentage of participants receiving solriamfetol were classified as ESS responders, as evidenced by having ≥ 25% improvement from baseline in ESS scores, or ESS remitters, as evidenced by achieving ESS scores within the normal range (≤ 10), compared with those receiving placebo. As found previously in analyses of the change from baseline in MWT or ESS scores,[20,21] the results of the current posthoc analyses of ESS responders seemed to be dose-dependent, such that more participants receiving the higher doses (150 mg and 300 mg) responded to treatment than those receiving the lower doses (37.5 mg and 75 mg); however, no statistical testing was conducted to compare responder rates across the dose groups.

At baseline, participants with narcolepsy had more severe EDS than participants with OSA, as evidenced by numerically

Figure 1—Cumulative distribution function plots: narcolepsy.

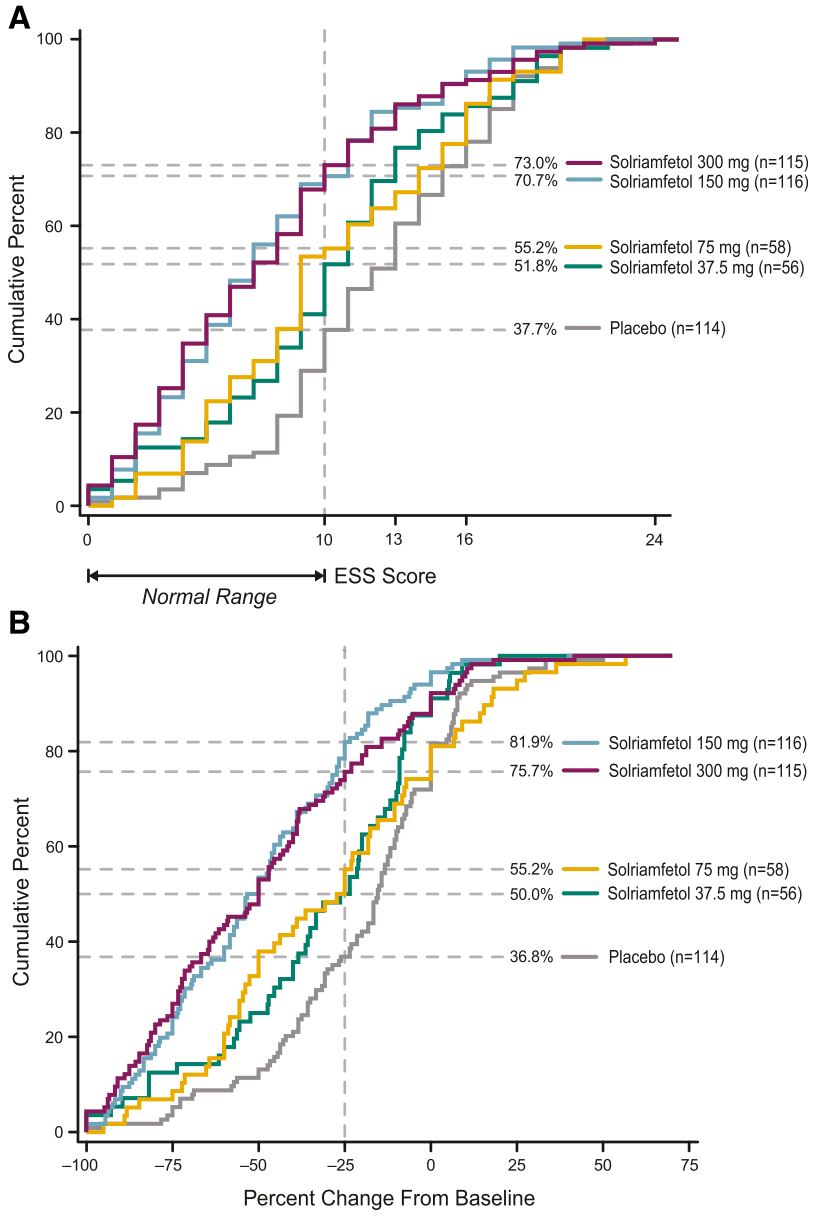


Cumulative distribution function plots for participants with narcolepsy at week 12 (mITT populations): percentages of participants with ESS score ≤ 10 **(A)** and with ≥ 25% decrease from baseline in ESS score **(B).** Vertical gray dashed lines represent thresholds for clinically meaningful improvement (ie, ESS ≤ 10 or > 25% decrease from baseline scores). Horizontal dashed lines indicate value at which each group reached the threshold (ie, percentage of participants who achieved each threshold). ESS = Epworth Sleepiness Scale, mITT = modified intent-to-treat.

higher ESS scores (**Table 1**). Although no formal testing was conducted to compare differences in baseline scores between populations, differences in the baseline severity of EDS likely impact absolute and relative responses on the ESS. For instance, a lower percentage of participants with narcolepsy achieved normal ESS scores vs participants with OSA, which is likely related to the greater underlying severity of EDS in the narcolepsy population on average.

The percentage of participants who were identified as ESS remitters (defined as those who achieved ESS scores within the normal range) in the current analysis was consistent with or greater than what has been reported for other wake-promoting agents. In participants with narcolepsy, 40% of participants who received the maximum approved dose of solriamfetol (150 mg) in the current analysis achieved ESS scores ≤ 10 compared with 16% of participants treated with placebo. In a 12-week study of armodafinil in participants with narcolepsy, 28% of those who received the maximum approved dose (250 mg)[13] achieved ESS scores < 10 compared with 7% of participants receiving placebo.[26] In a study of pitolisant in participants with narcolepsy, 39% of participants receiving pitolisant (up to 40 mg) achieved ESS scores ≤ 10 compared with 18% of participants

Figure 2—Cumulative distribution function plots: OSA.



Cumulative distribution function plots for participants with OSA at week 12 (mITT populations): percentages of participants with ESS score ≤ 10 **(A)** and with ≥ 25% decrease from baseline in ESS score **(B).** Vertical gray dashed lines represent threshold for clinically meaningful improvement (ie, ESS ≤ 10 or > 25% decrease from baseline scores). Horizontal dashed lines indicate value at which each group reached the threshold (ie, the percentage of participants who achieved each threshold). ESS = Epworth Sleepiness Scale, mITT = modified intent-to-treat, OSA = obstructive sleep apnea.

receiving placebo; however, this result was after 7 weeks of treatment (3 weeks of flexible dosing followed by 4 weeks of stable dosing) with doses higher than the maximum approved dose (17.8 mg).[14,27]

In participants with OSA, 71% of participants who received the maximum approved dose of solriamfetol (150 mg) in the current analysis achieved ESS scores ≤ 10 compared with 38% of participants treated with placebo. In a 12-week study of modafinil in participants with OSA, 38% of those who received the maximum approved dose (200 mg)[12] achieved ESS scores < 10, compared with 17% of participants receiving placebo.[28] In a 12-week study of pitolisant in participants with OSA who were refusing continuous positive airway pressure therapy, 67% of those receiving pitolisant achieved ESS scores ≤ 10, compared with 45% in the placebo group.[29] Note that these are indirect comparisons with differences in study populations and the methods used for data analyses. However, baseline ESS scores were similar across studies within the same patient population (narcolepsy or OSA). ESS responder analyses based on a clinically relevant percent improvement from baseline, such as the ≥ 25% reduction threshold evaluated in the current analysis, have not been investigated for other wake-promoting agents.

The current findings provide meaningful context for the established wake-promoting effects of solriamfetol treatment

Table 2—TEAEs (safety populations).

TEAE	Narcolepsy		OSA	
	Placebo (n = 59)	Solriamfetol, All Doses (n = 177)	Placebo (n = 119)	Solriamfetol, All Doses (n = 355)
Any TEAE, n (%)	27 (45.8)	121 (68.4)	57 (47.9)	241 (67.9)
Serious TEAE, n (%)	0	1 (0.6)	2 (1.7)	3 (0.8)
TEAE leading to study drug discontinuation, n (%)	1 (1.7)	9 (5.1)	4 (3.4)	26 (7.3)
Most common TEAEs, n (%)[a]				
Headache	3 (5.1)	38 (21.5)	10 (8.4)	36 (10.1)
Nausea	1 (1.7)	19 (10.7)	7 (5.9)	28 (7.9)
Decreased appetite	1 (1.7)	19 (10.7)	1 (0.8)	27 (7.6)
Nasopharyngitis	3 (5.1)	16 (9.0)	8 (6.7)	18 (5.1)
Dry mouth	2 (3.4)	13 (7.3)	2 (1.7)	16 (4.5)
Anxiety	1 (1.7)	9 (5.1)	0	25 (7.0)

[a]Reported in ≥ 5% of participants treated with solriamfetol (all doses) for either indication. OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event.

and are clinically informative despite several limitations. First, this was a posthoc analysis and, as such, the outcomes were not prespecified, the studies were not powered to evaluate these endpoints, and statistical comparisons between dose groups and indications were not performed. Therefore, the results reported here should be considered with those factors in mind. In addition, only scores from a self-reported measure of EDS, the ESS, were analyzed and, as such, these analyses do not speak to the clinical relevance of the impact of solriamfetol on objective measures of EDS, such as the MWT. However, a recent posthoc analysis of the test-retest reliability of the ESS from the two 12-week solriamfetol trials in participants with narcolepsy or OSA showed that the ESS has acceptable reliability.[30] Finally, the eligibility criterion for inclusion in the current studies was an ESS score ≥ 10, which allowed for the inclusion of a few participants with ESS scores of 10 (the lowest score considered to be within the normal range) at baseline.[22,23] Specifically, 2 (0.9%) participants with narcolepsy (75 mg, n = 1; 150 mg, n = 1) and 28 (6.1%) participants with OSA (placebo, n = 5; 37.5 mg, n = 3; 75 mg, n = 3; 150 mg, n = 9; 300 mg, n = 8) had ESS scores of 10 at baseline.

Overall, the results of this analysis showed the clinical relevance of the effects of solriamfetol in the treatment of EDS associated with narcolepsy or OSA, as evidenced by the higher percentage of participants receiving solriamfetol who reported ESS scores within the normal range and who had reductions (improvements) of ≥ 25% from baseline in ESS scores compared with placebo. The safety profile was similar between the narcolepsy and OSA populations.

ABBREVIATIONS

CI, confidence interval
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
MWT, Maintenance of Wakefulness Test
NNT, number needed to treat
OSA, obstructive sleep apnea
TEAE, treatment-emergent adverse event

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DISCLOSURE STATEMENT

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