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Randomized Controlled Trial of Solriamfetol for Excessive Daytime Sleepiness in OSA

An Analysis of Subgroups Adherent or Nonadherent to OSA Treatment

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BACKGROUND: Solriamfetol, a dopamine-norepinephrine reuptake inhibitor, is approved in the United States to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with OSA (37.5-150 mg/d).

RESEARCH QUESTION: Does solriamfetol have differential effects on EDS based on adherence to primary OSA therapy and does solriamfetol affect primary OSA therapy use?

STUDY DESIGN AND METHODS: Participants were randomized to 12 weeks of placebo or solriamfetol 37.5, 75, 150, or 300 mg/d (stratified by primary OSA therapy adherence). Coprimary end points were week 12 change from baseline in 40-min Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS) in the modified intention-to-treat population. Primary OSA therapy use (hours per night, % nights) and safety were evaluated.

RESULTS: At baseline, 324 participants (70.6%) adhered to OSA therapy (positive airway pressure use ≥ 4 h/night on ≥ 70% nights, surgical intervention, or oral appliance use on ≥ 70% nights) and 135 participants (29.4%) did not adhere. Least squares (LS) mean differences from placebo in MWT sleep latency (minutes) in the 37.5-, 75-, 150-, and 300-mg/d groups among adherent participants were 4.8 (95% CI, 0.6-9.0), 8.4 (95% CI, 4.3-12.5), 10.2 (95% CI, 6.8-13.6), and 12.5 (95% CI, 9.0-15.9) and among nonadherent participants were 3.7 (95% CI, –2.0 to 9.4), 9.9 (95% CI, 4.4-15.4), 11.9 (95% CI, 7.5-16.3), and 13.5 (95% CI, 8.8-18.3). On ESS, LS mean differences from placebo in the 37.5-, 75-, 150-, and 300-mg/d groups among adherent participants were –2.4 (95% CI, –4.2 to –0.5), –1.3 (95% CI, –3.1 to 0.5), –4.2 (95% CI, –5.7 to –2.7), and –4.7 (95% CI, –6.1 to –3.2) and among nonadherent participants were –0.7 (95% CI, –3.5 to 2.1), –2.6 (95% CI, –5.4 to 0.1), –5.0 (95% CI, –7.2 to –2.9), and –4.6 (95% CI, –7.0 to –2.3). Common adverse events included headache, nausea, anxiety, decreased appetite, nasopharyngitis, and diarrhea. No clinically meaningful changes were seen in primary OSA therapy use with solriamfetol.

INTERPRETATION: Solriamfetol improved EDS in OSA regardless of primary OSA therapy adherence. Primary OSA therapy use was unaffected with solriamfetol.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02348606; URL: www.clinicaltrials.gov; EU Clinical Trials Register; No.: EudraCT2014-005514-31; URL: www.clinicaltrialsregister.eu

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KEY WORDS: JZP-110; obstructive sleep apnea syndromes; sleep apnea

ABBREVIATIONS: AE = adverse event; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version; mITT = modified intention-to-treat; MWT = Maintenance of Wakefulness Test; PAP = positive airway pressure; PGI-C = Patient Global Impression of Change

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Take-home Points

Study Question: Does solriamfetol have differential effects on EDS based on adherence to primary OSA therapy and does solriamfetol affect primary OSA therapy use?

Results: In this randomized, double-blind, placebo-controlled, parallel-group trial, changes from baseline to week 12 in MWT results, ESS score, FOSQ-10 total score, and PGI-C after 12 weeks of solriamfetol treatment relative to placebo were similar among participants who were adherent and nonadherent to primary OSA therapy. No clinically meaningful changes in primary OSA therapy device use were observed over the 12-week study, as measured by the percentage of nights of device use, number of hours per night of device use, or percentage of nights with use of a device for more than half of the night.

Interpretation: Solriamfetol effectively treated EDS in patients with OSA regardless of adherence to primary OSA therapy and did not affect primary OSA therapy device use over the 12-week study.

Excessive daytime sleepiness (EDS) is common among individuals with OSA.[1,2] Positive airway pressure (PAP) or other airway therapies (eg, oral appliances, surgical procedures) are treatments for the underlying airway obstruction in OSA and subsequently reduce EDS in many patients.[3-5] However, despite adherence to these therapies and control of other factors that may contribute to pathologic sleepiness, EDS persists in some individuals. Specifically, residual EDS is reported by an estimated 9% to 22% of CPAP-treated patients in population-based studies.[6,7] In addition, other studies have shown that a substantial percentage of patients who use CPAP treatment for ≥ 7 h/night do not achieve normal responses on standard measures of sleepiness and functional outcomes.[3,5] Further, although patients with OSA may report symptom improvement, they may still have EDS and not be aware of their pathologic sleepiness.[5]

Several mechanisms, alone or in combination, likely contribute to EDS in OSA and to a continuance despite OSA treatment.[8] Animal models of sleep apnea suggest injury to wake-promoting neurons from intermittent hypoxia and persistence of sleep fragmentation,[9,10] whereas studies in humans demonstrate white matter structural differences in treated OSA patients with residual sleepiness compared with those without sleepiness.[11] Poor adherence to, or difficulty tolerating, PAP or other primary OSA treatment is common, resulting in reduced effectiveness and confounding the treatment intent.[12] Regardless of mechanism, consequences of EDS include impairments in cognitive function, work productivity, and quality of life, as well as risk for occupational and motor vehicle accidents. Thus, treatment of EDS is warranted, and some patients who remain sleepy despite efforts to treat other causes of pathologic sleepiness may benefit from wake-promoting pharmacologic treatment, as long as these drugs are not used as a substitute for primary OSA therapy.[13-17] Although previous studies of wake-promoting drugs used for treatment of residual sleepiness in CPAP-treated patients have not shown clinically relevant decreases in CPAP use,[18,19] the effect of any drug on adherence to primary OSA therapy is an important factor to evaluate given the consequences of untreated or inadequately treated OSA.

Solriamfetol, a dopamine-norepinephrine reuptake inhibitor,[20] is approved by the US Food and Drug Administration to improve wakefulness in adults with EDS associated with OSA (37.5-150 mg/d) or narcolepsy (75-150 mg/d)[21]; a positive opinion from the Committee for Medicinal Products for Human Use was received recommending European Medicines Agency approval for the same indications.[22] Solriamfetol demonstrated robust wake-promoting effects in a dose-dependent fashion in sleepy patients with OSA in a phase III study.[23] Unlike previous trials of wake-promoting agents that included only patients who were currently using CPAP at a specified level of adherence,[24,25] the phase III study of solriamfetol enrolled participants with current or prior use of primary airway therapy (eg, CPAP, oral appliance),

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including participants who showed suboptimal adherence to such therapy, to study a population more representative of patients with OSA in clinical practice.[12,26] Only individuals who had declined to try a primary OSA therapy were excluded from the study.[23] It was recognized that adherence level may impact efficacy; therefore, participants were stratified by adherence or nonadherence before randomization, and the randomization stratification factor was included in the statistical model as a fixed effect for the coprimary efficacy end points (Maintenance of Wakefulness Test [MWT] and Epworth Sleepiness Scale [ESS]). The randomization stratification factor was not significant for the MWT or the ESS, suggesting that baseline adherence to primary OSA therapy was not a significant predictor of outcome regarding the primary end points.[23]

Given that nonadherence to primary OSA therapy is common in the OSA population,[12] the question of whether to treat EDS in these patients is of clinical importance, as is the question of whether pharmacologic treatment for EDS has a differential effect in patients who are adherent or nonadherent to primary therapy. As such, interest arose in extending the prespecified analyses reported in the primary publication by further evaluating whether solriamfetol exerted a differential effect in participants who were adherent or nonadherent across all relevant outcomes and dose levels examined. To determine the clinical relevance of these efficacy findings, functional outcomes were assessed in both subgroups. In addition, because of the possibility that improvement in EDS may reduce motivation to use primary OSA therapy, the current analysis also examined whether treatment with solriamfetol affected use of primary OSA therapy over time. The hypothesis was that solriamfetol would have similar effects on EDS in subgroups of participants who adhered or did not adhere to primary OSA therapy and that solriamfetol would not affect use of primary OSA therapy.

Methods

Study Design and Participants

These exploratory analyses were based on data from the Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness (TONES) 3 study, which was part of the TONES phase III program. This was a 12-week, double-blind, randomized, placebo-controlled, parallel-group study (ClinicalTrials.gov Identifier: NCT02348606; EudraCT Identifier: 2014-005514-31) that evaluated the safety and efficacy of solriamfetol in the treatment of EDS in adult participants with OSA.[23] The study was approved by institutional review boards or ethics committees at each site and was performed in accordance with the tenets of the Declaration of Helsinki; all participants provided written informed consent. Study methods have been published[23] and are summarized briefly below.

Participants were men and women 18 to 75 years of age with a diagnosis of OSA (International Classification of Sleep Disorders, 3rd Edition, criteria[27]) and self-reported (with clinician concurrence) current or prior use of a primary OSA therapy. Participants were eligible if they currently were using a primary therapy (at any level of adherence), had used a primary therapy in the past for $\geq$ 1 month with $\geq$ 1 documented adjustment to the therapy (eg, different mask, pressure, or method), or had undergone a surgical intervention in an attempt to treat the underlying obstruction. Additional inclusion criteria were ESS[28] score of $\geq$ 10, mean sleep latency of $<$ 30 min on the 40-min MWT,[29] and usual nightly sleep of $\geq$ 6 h. Key exclusion criteria were EDS resulting from a cause other than OSA, occupation requiring nighttime or variable-shift work, medical condition or history that could affect patient safety or interfere with study assessments, use of over-the-counter or prescription medications that could affect evaluation of EDS, and having declined to try a primary OSA therapy.

Except for reporting of adverse events (AEs), all analyses were based on the modified intention-to-treat (mITT) population (ie, participants who received $\geq$ 1 dose of study medication and had a baseline and $\geq$ 1 postbaseline MWT or ESS score). AEs were summarized for the safety population (ie, participants who received $\geq$ 1 dose of study medication).

Randomization and Study Treatment

Participants were assigned randomly, stratified by adherence or nonadherence to primary OSA therapy (including PAP, oral pressure therapy, oral appliance, upper airway stimulator, and surgical intervention for airway obstruction), in a 1:1:2:2:2 ratio to treatment with solriamfetol 37.5, 75, 150, or 300 mg or placebo. All study personnel were blinded to study treatments; all study drugs were prepared in identical opaque gelatin capsules to ensure adequate blinding. Participants were instructed to take the assigned study drug once daily as a single oral dose in the morning (within 1 h of wakening) on an empty stomach.

Adherence or nonadherence to primary OSA therapy at baseline was based on average use during the period between the screening and baseline visits ($\leq$ 29 days). Participants were categorized as adherent if they had history of a surgical intervention deemed effective in treating the airway obstruction, PAP use $\geq$ 4 h/night on $\geq$ 70% of nights, or self-report (with investigator concurrence) of oral appliance use on $\geq$ 70% of nights.[30] Participants were categorized as nonadherent if they had device use at a level lower than that specified above, no use of a device at all, or treatment with a surgical intervention deemed no longer effective (in the absence of adherent device use). At study entry, participants were instructed to maintain their same primary OSA therapy throughout the study.

Outcomes

Coprimary end points were change from baseline to week 12 in MWT[29] mean sleep latency (as determined from the first four of five trials of a 40-min MWT) and ESS[28] score. The key secondary end point was the percentage of participants reporting improvement on the Patient Global Impression of Change (PGI-C)[31] at week 12. An additional secondary end point was change from baseline to week 12 on the Functional Outcomes of Sleep Questionnaire short version (FOSQ-10) total score.[32] Assessments also were conducted at weeks 1 and 4 for MWT and at weeks 1, 4, and 8 for ESS, FOSQ-10, and PGI-C, but are not reported here.

Safety and tolerability assessments included monitoring of AEs and vital signs at each study visit. At baseline and weeks 1, 4, and 12,

vital signs, including heart rate, systolic BP, and diastolic BP, were obtained at seven time points during the day from before dosing to approximately 9 h after dosing.

For participants using devices as primary OSA therapy (at any level of adherence), use during the study was recorded by electronic download (when available) or by diary. The following variables were summarized by analysis periods (baseline, defined as the period between screening and baseline visits [≤ 29 days]; weeks 1-4; weeks 5-8; and weeks 9-12): number of hours per night that participants used the device (from devices with electronically retrievable data), percentage of nights that participants reported use for more than half of the night (from diary data for those without electronically retrievable data), and percentage of nights that participants used the device (from electronically retrievable and diary data).

Statistical Analyses

Baseline demographic and disease characteristics are presented for the mITT population. Analyses of efficacy and primary OSA therapy use data were based on the mITT population.

Prespecified analyses of MWT and ESS in subgroups (adherent or nonadherent) were performed using a mixed-effects repeated measures model with fixed effects for treatment, time, treatment-by-time interaction, and baseline value of the efficacy end point. A similar model was used to analyze change from baseline in FOSQ-10 total score. Results are presented as least squares mean change from baseline and SE, with least squares mean differences from placebo and 95% CIs for the coprimary end points. To compare percentages of participants improving on PGI-C, χ^2 tests were used; 95% CIs were calculated for the differences in proportions. Post hoc analyses were conducted to evaluate the interaction of adherence and nonadherence with these key efficacy variables, including the MWT, ESS, FOSQ-10 score, and PGI-C score. Descriptive analyses were performed to summarize average hours of primary OSA therapy per night (electronically retrievable data), percentage of nights that participants used primary OSA therapy at least half the night (diary data), and percentage of nights that participants used the device (from electronically retrievable and diary data). For participants with electronically retrievable data, missing data were imputed using a modified last observation carried forward approach. The missing daily data were imputed by carrying forward the last nonmissing observation up to the early termination date or the date of the end of that analysis period (weeks 1-4, weeks 5-8, and weeks 9-12), whichever was earlier. A post hoc sensitivity analysis also was conducted in which missing data within the analysis period were imputed using zero to evaluate the impact of the handling of missing data on the outcome. For participants with diary data, only nonmissing data were summarized, and no imputation method was used for missing data. Change from baseline to each analysis after the baseline period in the percentage of nights that the primary OSA therapy was used, number of hours per night that the primary OSA therapy was used, and the percentage of nights that the primary OSA therapy was used for more than half the night were analyzed with a Wilcoxon rank-sum test to compare each treatment group vs placebo and a combined solriamfetol group vs placebo. No formal hypothesis testing was prespecified in the statistical analysis plan. The statistical testing conducted was considered exploratory. As such, no adjustments were made for multiplicity, and all reported *P* values are nominal.

Post hoc descriptive analyses were performed using the mITT population to summarize the percentage of participants in the adherent and nonadherent subgroups who had MWT sleep latencies of ≥ 20 min,[29] ESS scores of ≤ 10,[28] and FOSQ-10 total scores of ≥ 17.8[32] at baseline and week 12. ESS scores of ≤ 10 are considered within the normal range.[28,33] Cut off values for the MWT and FOSQ-10 score were selected because they are established values for the lower limit of normal. AEs were summarized for the safety population by adherence to primary OSA therapy.

Results

Participant Population

The first study participant was screened on May 19, 2015, and the last participant completed the study on December 23, 2016. Of the 474 participants in the safety population, 404 (85.2%) completed the study (Fig 1). A history of surgical intervention for OSA was reported in 14.6% of participants. At baseline, 344 of 474 participants (72.6%) in the safety population used a primary OSA therapy; of these, 318 of 344 participants (92.4%) used PAP, five of 344 participants (1.5%) used another type of primary OSA therapy device, and 21 of 344 participants (6.1%) did not specify the type of device they used. At study entry, 324 participants (70.6%) in the mITT population were considered adherent and 135 participants (29.4%) were considered nonadherent to primary OSA therapy. As expected, participants in the nonadherent subgroups showed higher apnea-hypopnea indexes and slightly lower mean MWT sleep latencies relative to the adherent subgroups (Table 1).

Efficacy of Solriamfetol by Adherence Subgroup

The overall pattern of changes from baseline to week 12 in MWT sleep latency and ESS scores was consistent between subgroups defined by adherence to primary OSA therapy at baseline. In both subgroups, solriamfetol increased MWT sleep latency in a dose-dependent manner relative to placebo (Fig 2). Likewise, solriamfetol treatment was associated with dose-dependent decreases in ESS score relative to placebo in both the adherent and nonadherent subgroups (Fig 3). An alternative model that included the treatment by adherence interaction term was run for the coprimary end points (MWT and ESS). The interaction term was not significant when comparing solriamfetol (combined doses) with placebo for either the MWT ($P = .32$) or ESS ($P = .97$), indicating no significant interaction occurred between adherence and treatment effect.

Higher percentages of participants taking solriamfetol reported overall improvement on the PGI-C relative to placebo, regardless of adherence to primary OSA therapy, with the exception of the nonadherent

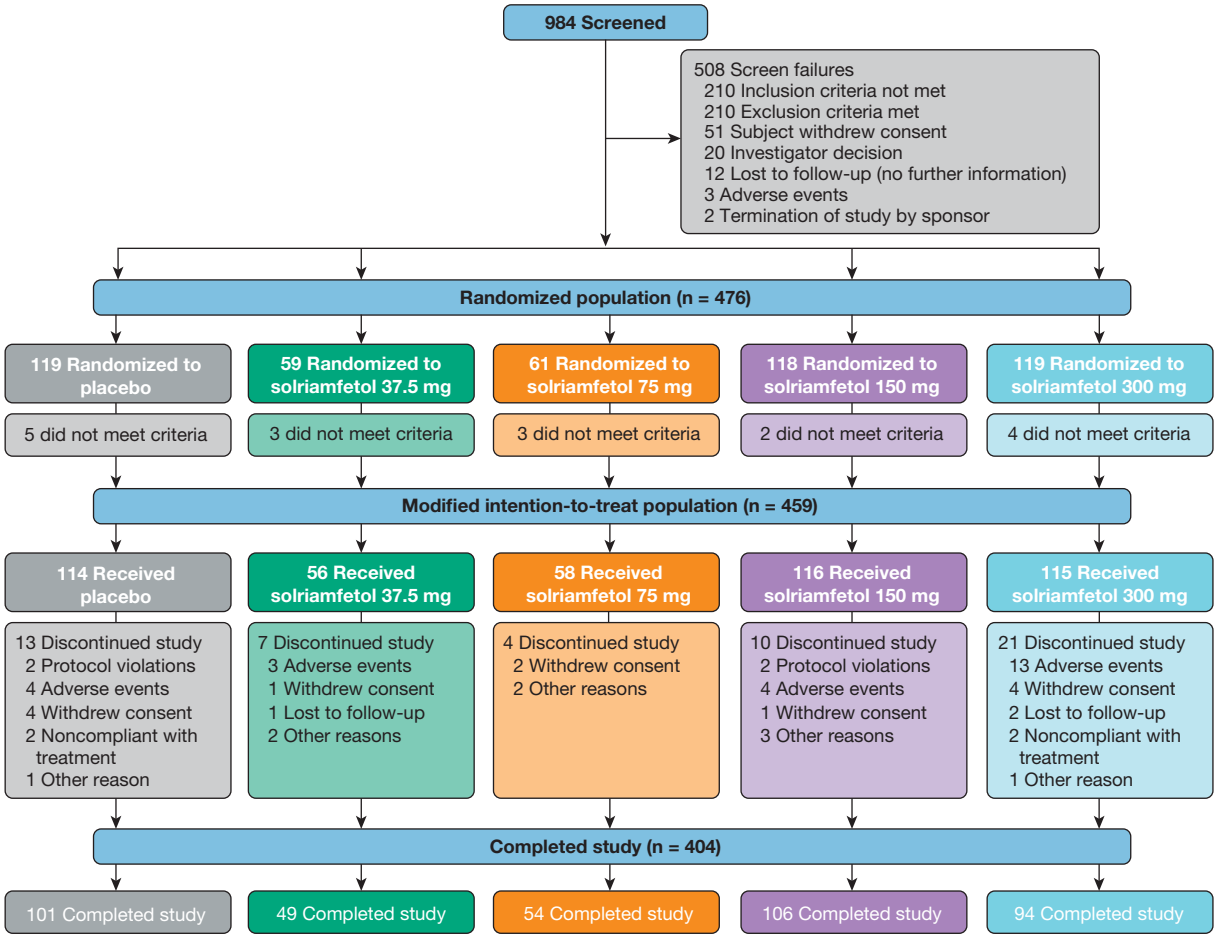

Figure 1 – *Flow chart showing participant disposition (Consolidated Standards of Reporting Trials Diagram). Fifteen participants in the randomized population did not have baseline or ≥ 1 postbaseline evaluation of Maintenance of Wakefulness Test sleep latency or Epworth Sleepiness Scale scores, and two participants did not receive solriamfetol. These participants did not meet the prespecified criteria for inclusion in the modified intention-to-treat population.*

subgroup taking the 37.5-mg dose (Fig 4). In both the adherent and nonadherent subgroups, FOSQ-10 total score increased from baseline to week 12 in a dose-dependent manner in all solriamfetol treatment groups relative to placebo (Fig 5). A Breslow-Day test for homogeneity and an alternative model that included the treatment by adherence interaction term were run for the PGI-C and FOSQ-10 end points, respectively. The test for homogeneity for the PGI-C ($P = .97$) and the interaction term for the FOSQ-10 ($P = .71$) were not significant when comparing solriamfetol (combined doses) with placebo, indicating no significant modification or interaction of adherence on treatment effect for these outcomes. At week 12, a greater percentage of participants taking solriamfetol (combined dose groups) achieved MWT mean sleep latencies of ≥ 20 min, ESS scores of ≤ 10, and FOSQ-10 total scores of ≥ 17.8 relative to placebo, regardless of adherence status (e-Table 1).

Effect of Solriamfetol on Primary Therapy Use

Changes in primary OSA therapy use throughout the 12-week study were minimal for the placebo and solriamfetol groups, as measured by the percentage of nights of device use, number of hours per night of device use, or percentage of nights with use of a device for more than half of the night (Table 2). Findings were similar for individual solriamfetol dose groups (e-Fig 1) and when an alternate method of handling missing data was used (e-Table 2).

Adverse Events by Adherence Subgroup

In both the adherent and nonadherent subgroups, a higher percentage of participants receiving solriamfetol experienced ≥ 1 AE compared with those receiving placebo. The incidences of AEs and discontinuations resulting from AEs generally were dose dependent, and AEs were mild or moderate in severity across subgroups.

TABLE 1] Baseline Demographics and Clinical Characteristics by Treatment Group and Adherence[a] to Primary OSA Therapy (mITT Population)

Variable	Placebo		Solriamfetol (Combined)	
	Adherent	Nonadherent	Adherent	Nonadherent
Baseline demographics				
No.	80	34	244	101
Age, y	54.5 (11.7)	52.9 (11.4)	54.6 (10.5)	52.0 (11.3)
Male sex, %	68.8	52.9	62.3	61.4
BMI, kg/m^2	33.4 (5.4)	32.5 (5.0)	33.8 (5.5)	32.2 (4.8)
Baseline clinical characteristics				
MSL on MWT, min[b]	13.2 (7.5)	11.2 (6.2)	13.4 (7.5)	10.4 (6.5)
95% CI	11.5-14.9	9.0-13.4	12.5-14.4	9.1-11.7
ESS score	15.3 (3.1)	16.1 (3.8)	14.9 (3.2)	15.6 (3.5)
95% CI	14.6-16.0	14.8-17.4	14.5-15.3	14.9-16.3
FOSQ-10 total score	13.2 (2.8)	14.1 (3.6)	14.1 (3.0)	13.9 (2.9)
95% CI	12.6-13.8	12.9-15.4	13.7-14.5	13.3-14.5
AHI[c]	5.6 (8.9)	23.4 (29.1)	3.9 (6.7)	17.2 (19.6)
95% CI	3.6-7.6	13.2-33.6	3.1-4.8	13.3-21.0

Data are presented as mean (SD), unless otherwise indicated. AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version; mITT = modified intention-to-treat; MSL = mean sleep latency; MWT = Maintenance of Wakefulness Test.
[a]Adherence at baseline was defined as effective surgical intervention, positive airway pressure use of ≥ 4 h/night on ≥ 70% of nights, or historical report (with investigator concurrence) of oral appliance use on ≥ 70% of nights.
[b]For baseline MSL on MWT, adherent placebo group, n = 77; nonadherent placebo group, n = 34; adherent solriamfetol group, n = 240; and nonadherent solriamfetol group, n = 99.
[c]For baseline AHI, adherent placebo group, n = 80; nonadherent placebo group, n = 34; adherent solriamfetol group, n = 242; and nonadherent solriamfetol group, n = 101.

Five participants, two (1.7%) randomized to placebo and three (0.8%) randomized to solriamfetol, experienced seven serious AEs. No deaths occurred. The most common treatment-emergent AEs (incidence ≥ 5% across solriamfetol doses) between the adherent and nonadherent subgroups included headache, nausea, anxiety, decreased appetite, nasopharyngitis, and diarrhea (Table 3). At week 12, solriamfetol was

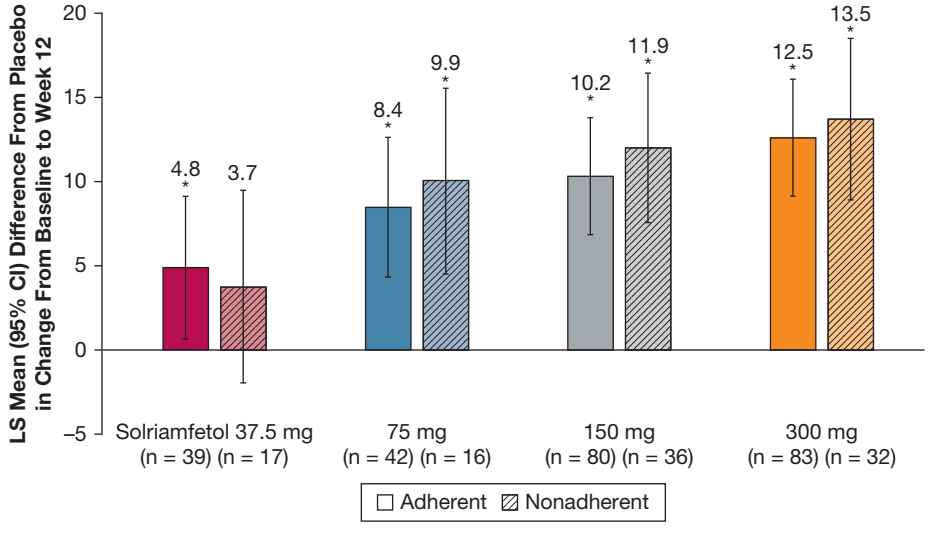

Figure 2 – *Bar graph showing the difference from placebo in change in Maintenance of Wakefulness Test score from baseline to week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). *P < .05 vs placebo. P values are nominal. LS = least squares.*

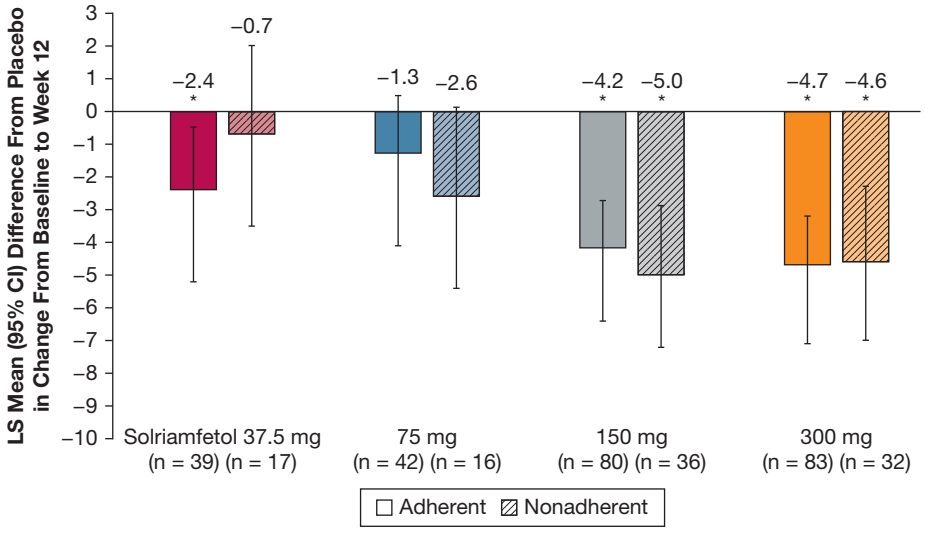

Figure 3 – *Bar graph showing the difference from placebo in change in Epworth Sleepiness Scale score from baseline to week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). *P < .05 vs placebo. Reported P values are nominal. LS = least squares.*

associated with small mean increases from baseline in heart rate, systolic BP, and diastolic BP relative to placebo in both the adherent and nonadherent subgroups (Table 4).

Discussion

In this study of adults with EDS associated with OSA, the effects of solriamfetol in treating EDS were similar in participants adherent and nonadherent to primary OSA therapy. The adherent and nonadherent subgroups both demonstrated dose-dependent improvements in MWT, ESS score, FOSQ-10 total score, and PGI-C over the 12-week study. Moreover, among individuals who used devices as primary OSA therapy at study entry, no clinically meaningful changes in device use occurred over the 12-week study.

Both subgroups demonstrated clinically meaningful changes in MWT, ESS, and FOSQ-10 values. In comparison with baseline, adherent and nonadherent subgroups taking solriamfetol demonstrated mean increases in MWT sleep latency ranging from 3.2 to 13.4 minutes, mean decreases in ESS score ranging from

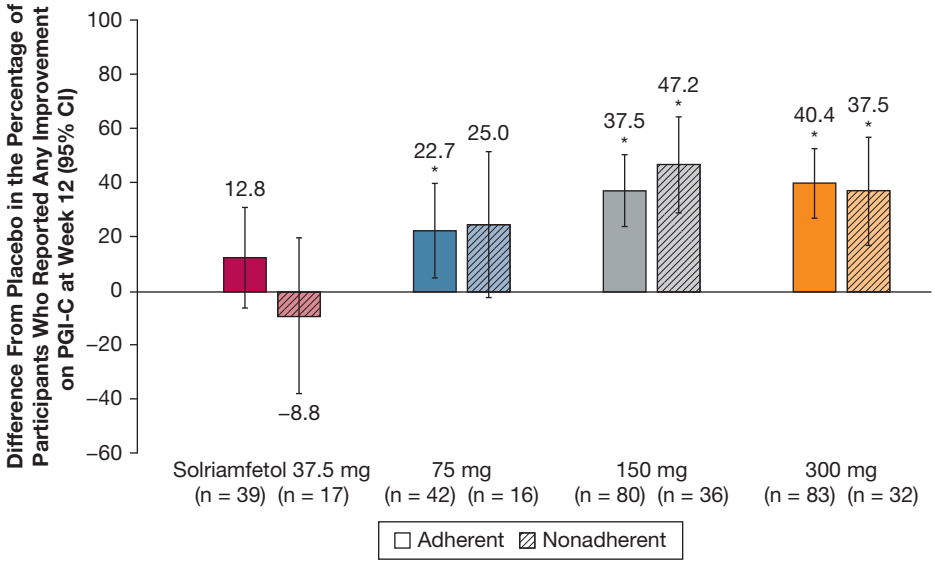

Figure 4 – *Bar graph showing the difference from placebo in the percentage of participants with improvement on the PGI-C scale at week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). *P < .05 vs placebo. Reported P values are nominal. PGI-C = Patient Global Impression of Change.*

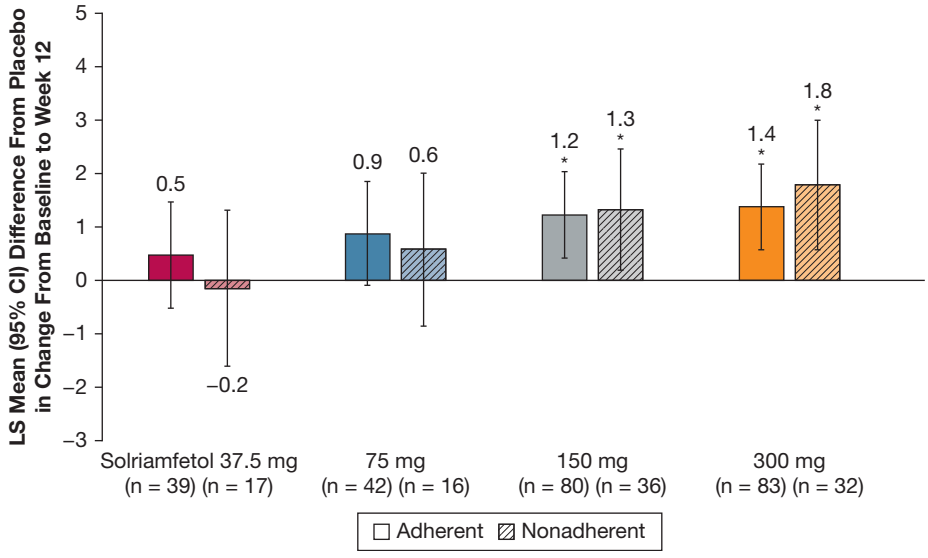

Figure 5 – *Bar graph showing the difference from placebo in change in Functional Outcomes of Sleep Questionnaire short version total score from baseline to week 12 in adherent and nonadherent subgroups (modified intention-to-treat population). *P < .05 vs placebo. Reported P values are nominal. LS = least squares.*

TABLE 2] Evaluation of Solriamfetol on Primary OSA Therapy Device Use[a]

Variable	Placebo (n = 81[b])		Solriamfetol (Combined; n = 255[c])	
	Median (IQR)	No.	Median (IQR)	No.
Nights primary OSA therapy device was used, %[d]				
Baseline[e]	100.0 (87.5-100.0)	81	100.0 (88.9-100.0)	255
Change wk 1-4[f]	0 (−1.4 to 4.2)	79	0 (0-3.7)	251
Change wk 5-8[f]	0 (0-4.2)	75	0 (0.0-5.2)	223
Change wk 9-12[f]	0 (0-4.2)	69	0 (0-3.3)	218
No. of hours per night primary OSA therapy device was used[g]				
Baseline[e]	6.8 (6.0-7.3)	53	6.5 (5.7-7.4)	157
Change wk 1-4[f]	−0.1 (−0.2 to 0.2)	51	−0.1 (−0.6 to 0.3)	152
Change wk 5-8[f]	−0.3 (−0.8 to 0.3)	45	−0.2 (−0.6 to 0.3)	132
Change wk 9-12[f]	−0.4 (−0.8 to 0.4)	43	−0.2 (−0.8 to 0.3)	133
Nights primary OSA therapy device was used for more than half the night, %[h]				
Baseline	100 (100-100)	28	100 (100-100)	100
Change wk 1-4[f]	0 (0-0)	28	0 (0-0)	99
Change wk 5-8[f]	0 (0-0)	28	0 (0-0)	91
Change wk 9-12[f]	0 (0-0)	24	0 (0-0)	84

For participants with electronically retrievable data, missing data on primary OSA therapy device use were imputed by the last observation carried forward method within each period. For participants with diary data, only nonmissing data were summarized and no imputation method was used for missing data. mITT = modified intention-to-treat.

[a]Primary OSA therapy devices included use of positive airway pressure, oral pressure therapy, oral appliance, or upper airway stimulator.

[b]Number of participants in mITT population placebo group using a primary OSA therapy device at baseline.

[c]Number of participants in mITT population combined solriamfetol group using a primary OSA therapy device at baseline.

[d]Includes all participants using a primary OSA therapy device at baseline (electronically downloadable and diary data).

[e]Based on average use during the period between the screening and baseline visits (≤ 29 days).

[f]$P > .05$ for combined solriamfetol vs placebo and for each solriamfetol dose group vs placebo (data not shown; Wilcoxon rank-sum test).

[g]Based on use by participants with electronically downloadable data only.

[h]Based on use recorded in diary (for participants without electronically downloadable data; only participants with nonmissing diary data are summarized).

TABLE 3] Safety and Tolerability (Safety Population)

Variable	Placebo		Solriamfetol (Combined)	
	Adherent	Nonadherent	Adherent	Nonadherent
No.	83	36	251	104
Overall				
Any TEAEs	45 (54.2)	12 (33.3)	165 (65.7)	76 (73.1)
Any serious TEAEs	2 (2.4)	0	2 (0.8)	1 (1.0)
Any TEAEs leading to study drug interruption	2 (2.4)	0	10 (4.0)	4 (3.8)
Any TEAEs leading to study drug or study withdrawal	4 (4.8)	0	17 (6.8)	8 (7.7)
Most common TEAEs (≥ 5%)				
Headache	10 (12.0)	0	28 (11.2)	8 (7.7)
Nausea	7 (8.4)	0	19 (7.6)	9 (8.7)
Anxiety	0	0	19 (7.6)	6 (5.8)
Decreased appetite	0	1 (2.8)	16 (6.4)	11 (10.6)
Nasopharyngitis	6 (7.2)	2 (5.6)	12 (4.8)	6 (5.8)
Diarrhea	1 (1.2)	0	10 (4.0)	7 (6.7)

Data are presented as No. (%), unless otherwise indicated. TEAE = treatment-emergent adverse event.

4.3 to 8.9 points, and mean increases in FOSQ-10 total score ranging from 1.5 to 3.5 points. These changes generally exceed the threshold values corresponding to clinically meaningful improvements (changes rated by patients or clinicians as at least minimally improved) of 4 min for the MWT[34] and four points for the ESS,[34] and the threshold for a minimal clinically important difference of 1.7 to 2.0 points on the FOSQ-10.[35] In fact, for most doses of solriamfetol, the data exceed threshold values corresponding to changes rated by patients or clinicians as much or very much improved of 7 min for the MWT and 6 points for the ESS.[34] Moreover, the magnitude of the improvement in wakefulness and functional status in both subgroups was substantial, as indicated by the high percentage of individuals who achieved MWT sleep latencies of ≥ 20 min (lower limit of normal[29]), ESS scores of ≤ 10 (within the normal range[28,33]), and FOSQ-10 total scores of ≥ 17.9 (lower limit of normal[32]) in the solriamfetol treatment groups (e-Table 1). In contrast, meta-analyses of randomized controlled trials of modafinil or armodafinil in PAP-adherent individuals with EDS showed increases in MWT sleep latency of 2.5 to 3.0 min and decreases in ESS score of 2.2 to 3.0 points.[19,36,37] However, directly comparing MWT outcomes from these meta-analyses with the current study has limitations, including differences in maximal test duration (20-30 min for most modafinil and armodafinil studies[36] vs 40 min for the current study).

Of the participants using devices as their primary OSA therapy (eg, CPAP), the use was high at baseline (median nightly use: placebo, 6.8 h; combined solriamfetol, 6.5 h), with clinically insignificant median decreases of 12 and 23 min in both the solriamfetol and placebo groups, respectively, from baseline to week 12, and median nightly use of ≥ 6 h for all solriamfetol dose groups for all periods. The placebo and intervention data are similar to those reported in trials of modafinil and armodafinil, which also enrolled pathologically sleepy individuals with OSA treated with PAP, and collectively suggest that improvement in alertness with a medication like solriamfetol does not negatively affect adherence to primary OSA therapy, such as CPAP.[19]

The adherent and nonadherent subgroups' incidences of AEs and discontinuations because of AEs were higher with solriamfetol than with placebo and generally were dose dependent. AEs typically were mild to moderate in intensity, and the most common AEs between the subgroups included headache, nausea, anxiety, decreased appetite, nasopharyngitis, and diarrhea.

Treatment of EDS is an important element of OSA management because EDS is associated with cognitive impairments, impaired quality of life, and a risk for accidents and may persist in a substantial number of patients despite effective treatment of the underlying

TABLE 4] Change From Baseline to Week 12 in Vital Signs (Safety Population)[a]

	Placebo		Solriamfetol (Combined)	
Vital Sign	Adherent (n = 83)	Nonadherent (n = 36)	Adherent (n = 251)	Nonadherent (n = 104)
No.	69	30	210	86
Heart rate, beats/min	−0.4 (0.6)	1.3 (1.0)	1.9 (0.4)	2.0 (0.6)
BP, mm Hg				
Systolic	0.1 (0.9)	−0.7 (1.5)	1.3 (0.6)	1.5 (0.9)
Diastolic	−0.5 (0.6)	1.3 (0.9)	0.7 (0.4)	0.8 (0.6)

Data are presented as mean (SEM), unless otherwise indicated.
[a]Averaged across before dosing to 9 h after dosing among participants with nonmissing values.

airway obstruction.[6,7,13-17] For these patients, a thorough evaluation of factors that may contribute to sleepiness is required, such as depression, use of sedating medications, insufficient sleep, and other sleep disorders. For patients nonadherent with PAP treatment, evaluation of optimal pressure, mask interface, and patient-reported symptoms is essential. Behavioral therapies and educational strategies hold promise for improving adherence, but comparative-effectiveness studies are needed to translate these methods into routine care.[38,39] Despite efforts to optimize adherence and treat other causes of EDS, some patients remain sleepy and may benefit from wake-promoting drugs, provided these drugs are not used as a substitute for primary OSA treatment. Indeed, data from this study underscore the benefit of primary OSA therapy in the treatment of EDS, because a greater proportion of solriamfetol-treated participants who were adherent to primary OSA therapy achieved normal values on measures of EDS relative to participants nonadherent to primary OSA therapy.

A limitation of this study is the exploratory nature of these analyses. Another limitation is missing device use data among some participants, which are reflected in the decreasing sample size over time in Table 2 and could be interpreted as participants staying in the study, but discontinuing use of their primary OSA therapy device. However, of these participants who stayed in the study but did not report use data, analysis showed that across parameters that measured primary OSA therapy device use (eg, number of hours per night), a consistently higher percentage of participants were treated with placebo who did not report data compared with participants treated with solriamfetol. This finding suggests that any discontinuation of device use was not secondary to improved alertness with solriamfetol. Additional limitations include the short (12-week) duration along with the instruction to participants to maintain their current level of primary OSA therapy use. Finally, lack of an active comparator limits the ability to compare these results with other wake-promoting therapies.

Interpretation

Solriamfetol was effective in the treatment of EDS in participants with OSA, regardless of adherence or nonadherence to primary OSA therapy, and treatment with solriamfetol did not alter participants' use of primary OSA therapy. No meaningful differences in the safety or tolerability profiles were observed in the adherent and nonadherent groups. The inclusion of participants who were adherent and nonadherent to primary OSA therapy enhances the generalizability of these results in the real-world setting.

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