CHEST

Solriamfetol for the Treatment of Excessive Sleepiness in OSA

A Placebo-Controlled Randomized Withdrawal Study

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BACKGROUND: Excessive sleepiness (ES) is a common symptom of OSA, which often persists despite primary OSA therapy. This phase III randomized withdrawal trial evaluated solriamfetol (JZP-110) for the treatment of ES in adults with OSA.

METHODS: After 2 weeks of clinical titration (n = 174) and 2 weeks of stable dose administration (n = 148), participants who reported improvement on the Patient Global Impression of Change (PGI-C) and had numerical improvements on the Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS) were randomly assigned to placebo (n = 62) or solriamfetol (n = 62) for 2 additional weeks. Coprimary end points were change from weeks 4 to 6 in MWT and ESS.

RESULTS: In the modified intention-to-treat population (n = 122), MWT mean sleep latencies and ESS scores improved from baseline to week 4 (from 12.3-13.1 to 29.0-31.7 minutes and from 15.3-16.0 to 5.9-6.4, respectively). From weeks 4 to 6, participants treated with solriamfetol maintained improvements (least squares [LS] mean [SE] changes of −1.0 [1.4] minutes on MWT and −0.1 [0.7] on ESS), whereas participants treated with placebo worsened (LS mean [SE] change of −12.1 [1.3] minutes on MWT and 4.5 [0.7] on ESS); LS mean differences between treatments were 11.2 minutes (95% CI, 7.8-14.6) and −4.6 (95% CI, −6.4 to −2.8) on MWT and ESS, respectively. Fewer participants treated with solriamfetol reported worsening on the PGI-C from weeks 4 to 6 (20% vs 50%; $P = .0005$). Common adverse events included headache, dry mouth, nausea, dizziness, and insomnia.

CONCLUSIONS: This study demonstrated maintenance of solriamfetol efficacy and safety over 6 weeks.

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ABBREVIATIONS: CGI-C = Clinical Global Impression of Change; ES = excessive sleepiness; ESS = Epworth Sleepiness Scale; FOSQ-10 = 10-item Functional Outcomes of Sleep Questionnaire; LS = least squares; mITT = modified intention to treat; MWT = Maintenance of Wakefulness Test; PGI-C = Patient Global Impression of Change

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Excessive sleepiness (ES), one of the main presenting symptoms of OSA, is estimated to persist in 12% to 65% of individuals receiving CPAP therapy.[1-4] The effect of ES on individuals with OSA includes functional impairment, reduced quality of life, and increased risk for occupational and motor vehicle accidents.[5-9]

Solriamfetol (formerly known as JZP-110 and ADX-N05) is a selective dopamine and norepinephrine reuptake inhibitor with robust wake-promoting effects. Its mechanism of action differs from those of amphetamines, modafinil, and armodafinil.[10] Solriamfetol demonstrated significant efficacy relative to placebo for reducing ES and increasing wakefulness in clinical trials of narcolepsy.[11-13] Efficacy for ES in OSA also was demonstrated by solriamfetol in a 12-week randomized, controlled phase III study.[14] This phase III trial evaluated the maintenance of efficacy and safety of solriamfetol administered once daily compared with placebo for the treatment of ES in adults with OSA.

Methods

Study Design

This was a clinical trial from the Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) phase III program, the TONES 4 study. This phase III, double-blind, placebo-controlled trial was performed from May 2015 to November 2016 in Finland, France, Germany, Sweden, and the United States. An enriched, randomized withdrawal design was used. The study was approved by the appropriate institutional review boards or independent ethics committees (e-Appendix 1) and was conducted in accordance with the amended Declaration of Helsinki; all participants provided written informed consent (ClinicalTrials.gov identifier NCT02348619; EudraCT number 2014-005515-16).

The study consisted of three phases (Fig 1). Participants started with a once-daily oral dose of 75 mg of solriamfetol; had the dose titrated up or down one dose level every 3 days to 75, 150, or 300 mg to maximize efficacy and tolerability in the titration phase (weeks 1 and 2); and continued this dose during the stable dose phase (weeks 3 and 4). The stable dose phase was followed by the double-blind randomized withdrawal phase (weeks 5 and 6). For this phase, participants who reported "much" or "very much" improvement on the Patient Global Impression of Change (PGI-C) scale and who had numerical improvement on the Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS) at week 4 were randomly assigned 1:1 to either receive placebo or continue their stable dose of solriamfetol. The randomization was stratified by participants' adherent or nonadherent use of a primary OSA therapy. An automated system was used to randomly assign participants.

Population

Participants were adults (age range, 18-75 years) with OSA diagnosed according to International Classification of Sleep Disorders-3 criteria[15] who had current or prior primary OSA therapy including CPAP, oral appliance, or surgical intervention. Additional inclusion criteria were BMI 18 to < 45 kg/m^2; baseline ESS score ≥ 10 and mean sleep latency < 30 minutes on the first four trials of a five-trial, 40-minute MWT; and usual nightly sleep time ≥ 6 hours.

Key exclusion criteria were any disorder other than OSA associated with ES; an occupation requiring nighttime shift work or variable shift work; excessive caffeine use 1 week prior to the study or nicotine dependence with a reported effect on sleep; presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect participant safety or interfere with study assessments; and use of any over-the-counter or prescription medications that could affect ES evaluation within a period corresponding to at least 5 half-lives of the drug. Pregnant, breastfeeding, or lactating women were excluded.

Outcomes

Coprimary end points were changes from week 4 to week 6 in MWT mean sleep latency and ESS score. The MWT is an objective measure of a participant's ability to maintain wakefulness,[16] and the ESS is a patient-reported outcome that assesses the propensity to fall asleep in different situations.[17] The MWT mean sleep latency, scored by a central reader (Clinilabs), was derived from the first four trials of a 40-minute, five-trial MWT. The mean of the first four MWT trials is a well-established regulatory end point that has been used in prior pivotal studies and was the prespecified coprimary end point in this study. A fifth MWT trial was included for exploratory analyses to evaluate effects later in the day, and those data are not reported here. The MWT was performed following published guidelines[18] at baseline, week 4, and week 6 after performance of overnight polysomnography at the study site.

The key secondary end point was the percentage of participants who reported worsening of their condition on the PGI-C from week 4 to week 6. The percentage of participants who worsened from week 4 to week 6 as reported by physicians on the Clinical Global Impression of Change (CGI-C) scale[19] was another secondary end point. The PGI-C and CGI-C are assessed using a 7-point scale from 1, indicating very much improved, to 7, indicating very much worse.[19]

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*Collaborators from the Tones 4 Study Investigators group are listed in the Acknowledgments.

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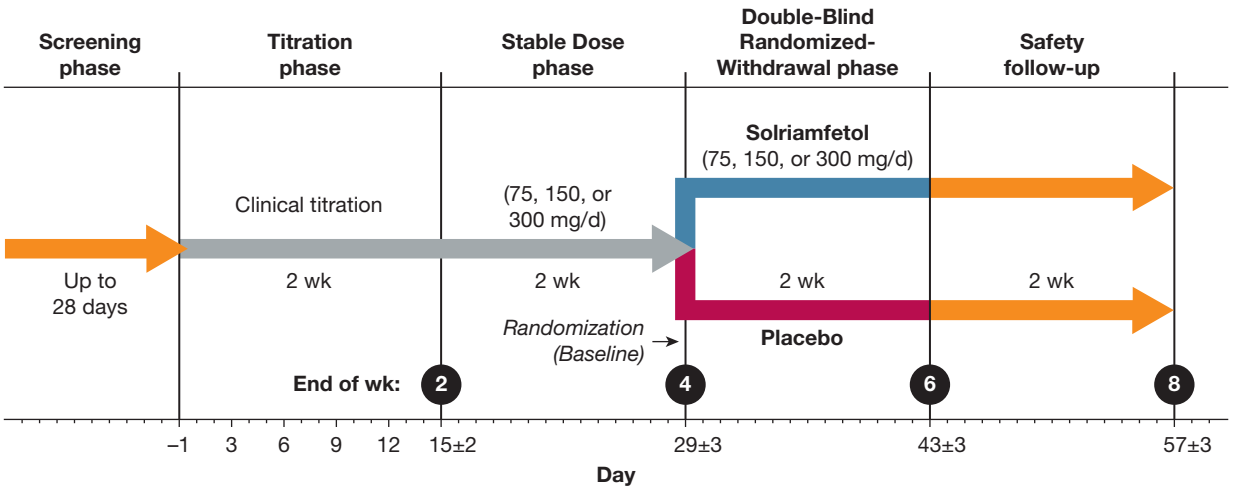


Figure 1 – *Study design. In the titration phase, participants started with 75 mg of solriamfetol once daily and were able to titrate up or down every 3 days to 75, 150, or 300 mg to maximize the therapeutic efficacy of solriamfetol at a safe and well-tolerated dose.*

Participant-reported daily function was assessed using the 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10),[20] which measures functional status for disorders of ES. Changes in FOSQ-10 total score were evaluated from the beginning of the titration phase to end of the stable dose phase (week 4) and from end of the stable dose phase to end of the double-blind randomized withdrawal phase (week 6), which was a secondary efficacy end point.

Evaluation of safety was based on the incidence of adverse events reported by the participants or noted by the investigator. The safety evaluation included laboratory assessments, measurement of vital signs, electrocardiograms, and risk of suicidality, evaluated at each study visit by using the Columbia-Suicide Severity Rating Scale.[21] On the days when the MWT was performed, BP and heart rate measurements were collected at seven time points throughout the day. The average of these time points from before administration of the dose to 9 hours after administration of the dose was used for evaluating change from baseline.

Analyses

Approximately 200 participants were planned for enrollment to ensure at least 122 participants in the randomized withdrawal phase. These sample sizes were based on a minimum of 61 participants per treatment group to provide at least 90% power to detect differences of 6 minutes in the MWT mean sleep latency time (mean of the first four trials) and 3.5 points in ESS changes from the beginning to the end of the randomized withdrawal phase. This calculation assumed SDs of 9.5 minutes and 5 points for changes in the MWT and ESS, respectively, during the randomized withdrawal phase and a two-sided significance level of .05 with use of a *t* test.

Analyses were performed on the modified intention-to-treat (mITT) population, defined as participants who were randomly assigned who received at least one dose of study medication and who had an MWT or ESS assessment at week 4 and at least one assessment after week 4. A last-observation-carried-forward approach was used for early withdrawals. An analysis of covariance model was used for the coprimary end points, with treatment group, measurement at week 4, and random assignment stratification factor as fixed effects. A χ^2 analysis was used for PGI-C and CGI-C. A fixed hierarchical testing procedure (coprimary and key secondary end points) was used to control for multiplicity,[22] starting with the comparison of solriamfetol vs placebo for the coprimary efficacy end points MWT and ESS, followed by the PGI-C if both coprimary end points were significant. All analyses were performed using software (SAS version 9.3; SAS Institute).

Results

Study Population

Of 174 participants enrolled into the titration phase, 71% (n = 124) were randomly assigned to placebo or solriamfetol in the double-blind randomized withdrawal phase (Fig 2).[23] There were 17 study discontinuations (10%) during the titration phase, six of which were due to adverse events. During the stable dose phase (n = 157), nine participants (6%) discontinued, and 24 participants did not enter the randomized withdrawal phase, of whom 21 (13%) were for not meeting the criteria for improvement. Two participants randomly assigned to solriamfetol discontinued during the randomized withdrawal phase; the final mITT population consisted of 62 participants randomly assigned to placebo and 60 to solriamfetol.

In the stable dose phase, 14.6%, 31.8%, and 53.5% of participants received the 75-, 150-, and 300-mg doses of solriamfetol, respectively. Of the 62 participants randomly assigned to solriamfetol in the randomized withdrawal phase, 14.5%, 41.9%, and 43.5% received 75, 150, and 300 mg, respectively.

Baseline characteristics of the safety population (ie, any participant who received at least one dose of solriamfetol in the titration phase) were consistent across the three phases of the study and were comparable between groups

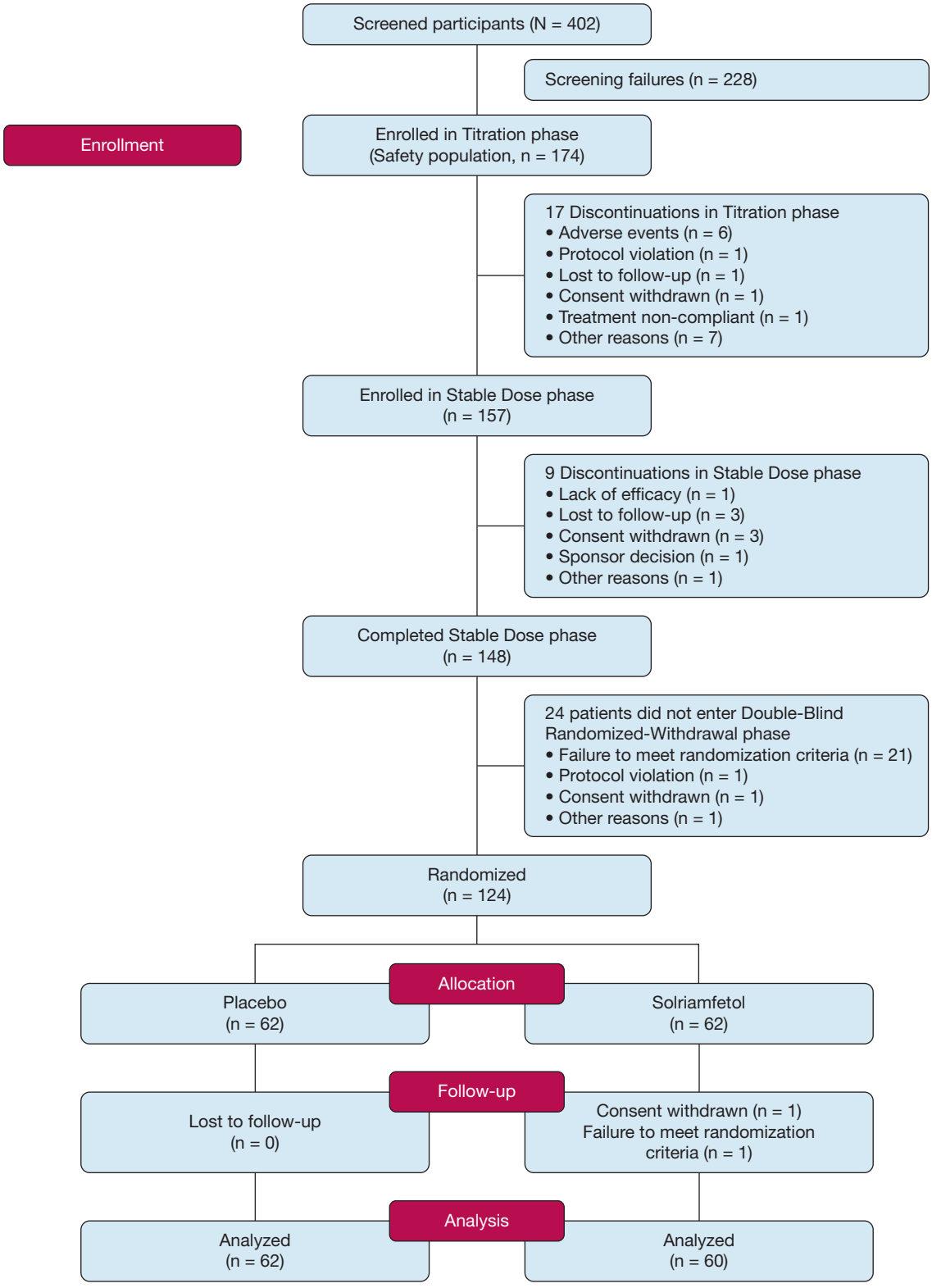


Figure 2 – *Consolidated Standards of Reporting Trials participant disposition.*[23]

(Table 1). Most participants (65.5%) were classified as moderately ill or markedly ill by their physicians on the Clinical Global Impression-Severity scale, and 71.3% were using a primary OSA therapy at baseline.[19] Baseline characteristics were also similar between the safety and the mITT populations (data not shown).

TABLE 1] Baseline Demographic and Clinical Characteristics of the Safety Population

Variable	All Solriamfetol Doses		Double-Blind Randomized Withdrawal Phase	
	Titration Phase	Stable Dose Phase	Placebo	All Solriamfetol Doses
No. of participants	174	157	62	62
Age, mean ± SD, y	54.8 ± 10.5	55.4 ± 10.2	56.2 ± 9.8	56.3 ± 11.4
Male, No. (%)	107 (61.5)	97 (61.8)	41 (66.1)	36 (58.1)
Race, No. (%)				
White	137 (78.7)	121 (77.1)	45 (72.6)	50 (80.6)
Black	34 (19.5)	34 (21.7)	15 (24.2)	12 (19.4)
Other	3 (1.7)	2 (1.3)	2 (3.2)	0
BMI, mean ± SD, kg/m^2	33.3 ± 5.4	33.3 ± 5.2	33.3 ± 5.5	32.9 ± 5.0
MWT, mean ± SD, min	13.2 ± 7.5	12.9 ± 7.1	12.3 ± 7.9	13.0 ± 6.7
ESS score, mean ± SD	15.4 ± 3.4	15.5 ± 3.5	16.0 ± 3.5	15.3 ± 3.5
CGI-S, No. (%)				
1 = Normal	0	0	0	0
2 = Borderline ill	6 (3.4)	6 (3.8)	3 (4.8)	2 (3.2)
3 = Mildly ill	21 (12.1)	18 (11.5)	7 (11.3)	6 (9.7)
4 = Moderately ill	71 (40.8)	61 (38.9)	23 (37.1)	23 (37.1)
5 = Markedly ill	43 (24.7)	41 (26.1)	15 (24.2)	20 (32.3)
6 = Severely ill	28 (16.1)	26 (16.6)	11 (17.7)	10 (16.1)
7 = Among the most extremely ill	5 (2.9)	5 (3.2)	3 (4.8)	1 (1.6)
Use of a primary OSA therapy, No. (%)	124 (71.3)	119 (75.8)	47 (75.8)	49 (79.0)

Percentages may not total 100% because of rounding. CGI-S = Clinical Global Impression-Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test.

Efficacy

Mean sleep latency on the MWT in the mITT population increased after 4 weeks of treatment, from approximately 12 to 13 minutes to approximately 30 minutes (Fig 3A), and participant-reported ES decreased from approximately 15 or 16 to approximately 6 (Fig 3B), which is within the normal range. During the subsequent randomized withdrawal phase (from week 4 to week 6), participants who continued solriamfetol had efficacy maintained, with negligible changes on both measures, whereas participants who were switched to placebo had worsened MWT and ESS scores (Fig 4). The difference between treatments for these observed changes was statistically significant for both measures. The least squares (LS) mean (SE) change in MWT mean sleep latency was −12.1 (1.3) minutes with placebo compared with −1.0 (1.4) minute with solriamfetol (Fig 4A); LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8-14.6; $P < .0001$). The LS mean changes in ESS score were 4.5 (0.7) and −0.1 (0.7) for placebo and solriamfetol, respectively (Fig 4B), resulting in an LS mean difference of −4.6 (95% CI, −6.4 to −2.8; $P < .0001$). Results on the MWT and ESS were similar in the subgroups of patients who were adherent or nonadherent with a primary OSA therapy, with slightly larger mean differences in the nonadherent subgroup (Table 2). Comparisons between the placebo and combined solriamfetol treatment groups during the randomized withdrawal phase showed statistical significance favoring solriamfetol ($P < .05$) for both subgroups of patients (ie, adherent and nonadherent with a primary OSA therapy) (Table 2).

During the randomized withdrawal phase, a statistically significant 50.0% of participants who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (−30.0; 95% CI, −46.0 to −14.0; $P < .001$) (Fig 5). Similarly, 59.0% of participants switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (−37.3; 95% CI, −53.50 to −21.19; $P < .0001$) (Fig 5). Results on the PGI-C and CGI-C were similar in the subgroups of patients who were adherent or nonadherent with a primary OSA therapy, with slightly larger differences from placebo in the nonadherent subgroup (Table 2). Comparisons between the placebo and combined solriamfetol

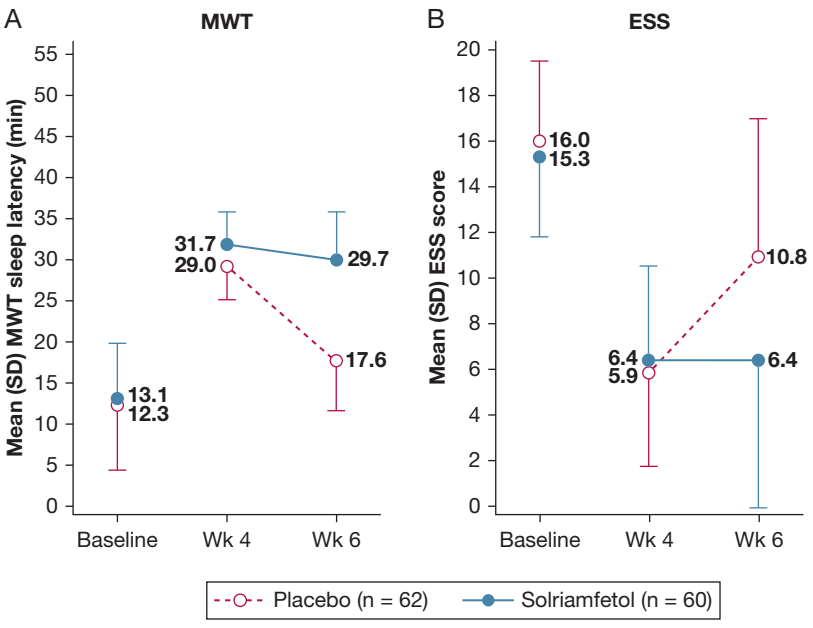


Figure 3 – *Values for the coprimary end points among participants who entered the double-blind randomized withdrawal phase (modified intention-to-treat population; n = 122). A, Maintenance of Wakefulness Test (MWT). B, Epworth Sleepiness Scale (ESS).*

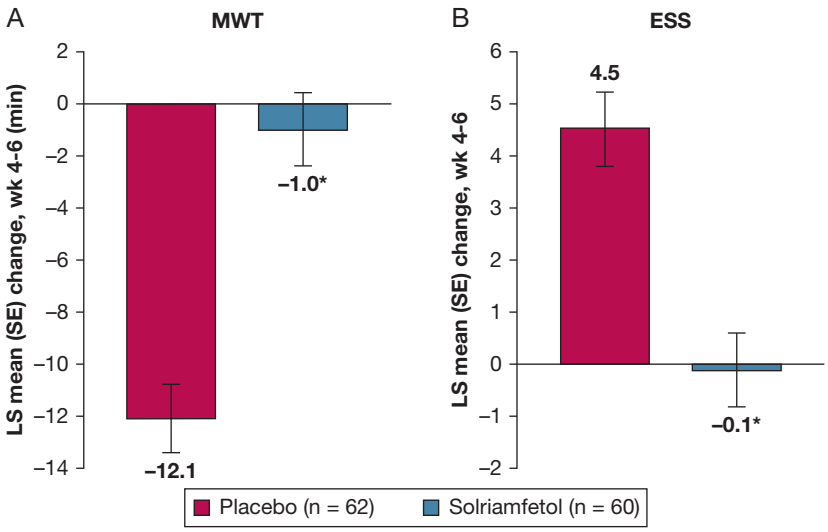
treatment groups during the randomized withdrawal phase were statistically significant in favor of solriamfetol ($P < .05$) for patients who were adherent and those who were nonadherent with a primary OSA therapy (Table 2).

Functional outcomes (ie, FOSQ-10 total score) improved from mean baseline scores of 13.5 to 13.7 to mean scores of 17.6 to 17.8 after 4 weeks of treatment (Fig 6). At the end of the randomized withdrawal phase (week 6), mean ± SD FOSQ-10 scores were 16.4 ± 2.9 in the placebo group and 17.4 ± 3.0 with solriamfetol (Fig 6), resulting in LS mean (SE) changes of −1.3 (0.4) and −0.2 (0.4), respectively; the LS mean difference significantly favored solriamfetol (1.2; 95% CI, 0.2-2.1; $P < .05$).

Safety

There were no deaths and no findings of suicidality on the Columbia-Suicide Severity Rating Scale during the study. The incidence of adverse events during the titration and stable dose phases is shown in Table 3 and by group in the randomized withdrawal phase in Table 4.

There were no serious adverse events during the study, and all withdrawals due to adverse events (3.4% of participants; n = 6) occurred during the titration phase;



*P < .0001 vs placebo.

Figure 4 – *Change from week 4 to week 6 for the coprimary end points in the double-blind randomized withdrawal phase (modified intention-to-treat population; n = 122). A, MWT. B, ESS. LS = least squares. See Figure 3 legend for expansion of other abbreviations.*

TABLE 2] Efficacy End Points at Week 6 Stratified by Adherent Use of a Primary OSA Therapy

Efficacy End Point	Adherent Use of Primary OSA Therapy		Nonadherent Use of Primary OSA Therapy	
	Placebo (n = 48)	Combined Solriamfetol (n = 48)	Placebo (n = 14)	Combined Solriamfetol (n = 12)
Change in MWT, min				
LS mean (SE)	−11.9 (1.4)	−2.1 (1.4)	−12.7 (2.0)	3.1 (2.2)
LS mean difference (95% CI)	…	9.8 (5.8-13.9)	…	15.7 (9.5-22.0)
P value	…	< .0001	…	< .0001
Change in ESS score				
LS mean (SE)	4.2 (0.7)	0.6 (0.7)	6.7 (1.08)	−1.7 (1.2)
LS mean difference (95% CI)	…	−3.6 (−5.7 to −1.5)	…	−8.4 (−11.7 to −5.1)
P value	…	.0010	…	< .0001
PGI-C				
Reported as worse, No. (%)[a]	23 (47.9)	12 (25.0)	8 (57.1)	0
Difference from placebo, % (95% CI)	…	−22.9 (−41.6 to −4.2)	…	−57.1 (−83.1 to −31.2)
P value	…	.0197	…	.0016
CGI-C				
Reported as worse, No. (%)[a]	25 (53.2)[b]	12 (25.0)	11 (78.6)	1 (8.3)
Difference from placebo, % (95% CI)	…	−28.2 (−47.0 to −9.4)	…	−70.2 (−96.8 to −43.7)
P value	…	.0048	…	.0003

CGI-C = Clinical Global Impression of Change; LS =least squares; PGI-C = Patient Global Impression of Change. See Table 1 legend for expansion of other abbreviations.
[a]Defined as minimally worse, much worse, or very much worse as measured from efficacy baseline (week 4) to week 6.
[b]n = 47 due to missing data for one participant.

the most frequent events leading to withdrawal were headache and palpitations, each reported for two participants. There was a higher incidence of adverse events during the titration phase (48.9%) than during the stable dose phase (10.2%), and the incidence of adverse events increased by dose, suggesting a dose response (data not shown). The most common adverse events (≥ 5%) during the titration phase included headache (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), and insomnia (5.7%), and the

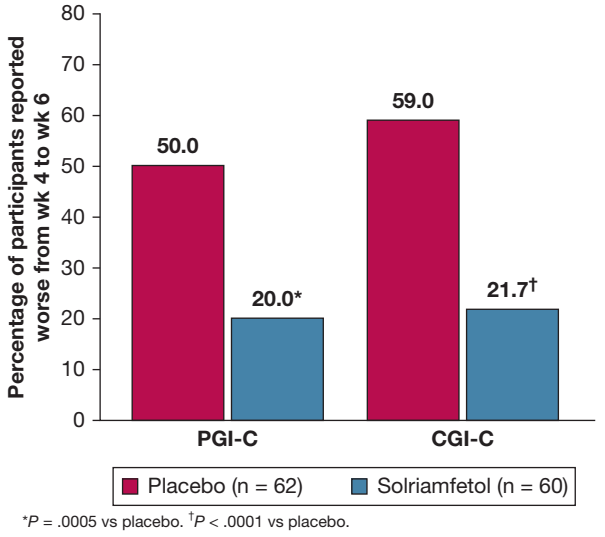


Figure 5 – *Percentage of participants who had overall worsening of their condition in the double-blind randomized withdrawal phase (modified intention-to-treat population; n = 122). CGI-C = Clinical Global Impression of Change; PGI-C = Patient Global Impression of Change.*

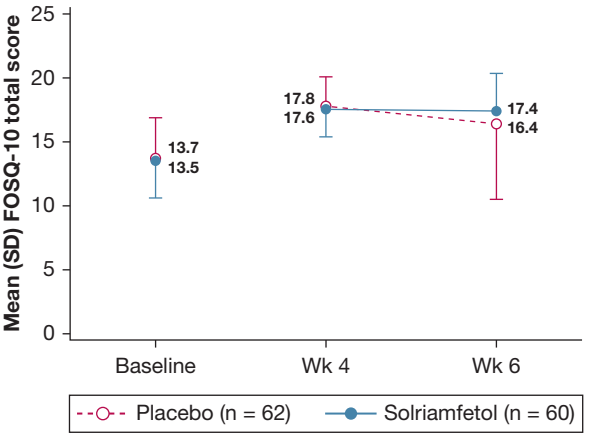


Figure 6 – *Total score for the 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10) among participants who entered the double-blind randomized withdrawal phase (modified intention-to-treat population; n = 122).*

TABLE 3] Adverse Events Occurring in the Open-Label Titration and Stable Dose Phases in the Safety Population

Variable	All Solriamfetol Doses	
	Titration Phase	Stable Dose Phase
No. of participants	174	157
Participants with at least 1 adverse event	85 (48.9)	16 (10.2)
Participants with at least 1 serious adverse event	0	0
Participants with at least 1 adverse event leading to withdrawal	6 (3.4)	0
Adverse events[a]		
Headache	17 (9.8)	2 (1.3)
Dry mouth	12 (6.9)	1 (0.6)
Nausea	12 (6.9)	1 (0.6)
Dizziness	10 (5.7)	3 (1.9)
Insomnia	10 (5.7)	1 (0.6)
Palpitations	8 (4.6)	1 (0.6)
Anxiety	7 (4.0)	1 (0.6)
Dyspepsia	4 (2.3)	0
Diarrhea	4 (2.3)	0

Data are presented as No. (%) unless otherwise stated.
[a]Adverse events are listed for those that occurred in at least 5% of participants in any treatment group.

TABLE 4] Adverse Events Occurring During the Double-Blind Randomized Withdrawal Phase

Variable	Placebo	All Solriamfetol Doses
No. of participants	62	62
Participants with at least 1 adverse event	6 (9.7)	18 (29.0)
Participants with at least 1 serious adverse event	0	0
Participants with at least 1 adverse event leading to withdrawal	0	0
Adverse events[a]		
Nasopharyngitis	0	3 (4.8)
Aphthous stomatitis	0	1 (1.6)
Upper respiratory tract infection	0	1 (1.6)
Cough	0	1 (1.6)

Data are presented as No. (%) unless otherwise stated.
[a]Adverse events are listed for those that occurred in at least 5% of participants in any treatment group.

incidence of these common adverse events was lower (0.6%-1.3%) during the stable dose phase (Table 3).

During the randomized withdrawal phase, 29.0% of participants who continued using solriamfetol experienced any adverse event relative to 9.7% of those switched to placebo. Nasopharyngitis was the most frequent adverse event (4.8%), and there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.

The mean changes in vital signs obtained before administration of the dose to 9 hours after administration of the dose on MWT days, across solriamfetol doses, were small increases from baseline to week 6 in systolic (mean ± SD change of 1.6 ± 8.7 mm Hg) and diastolic (0.8 ± 5.3 mm Hg) BP, as well as heart rate (1.0 ± 6.1 beats per minute). In the randomized withdrawal phase, small changes in BP (−1.5 ± 7.6 mm Hg for systolic and −0.5 ± 4.3 mm Hg for diastolic) and heart rate (0.2 ± 5.9 beats per minute) were observed in participants randomly assigned to placebo.

Discussion

This study further supports the previously demonstrated efficacy of solriamfetol for the treatment of ES in OSA by demonstrating that improvements in objective wakefulness and subjective sleepiness were maintained relative to worsening of these measures after discontinuation of solriamfetol among participants randomly assigned to placebo. Additionally, the results showed that abrupt discontinuation of the drug did not result in rebound hypersomnia or withdrawal-related adverse events.

The ability to treat ES effectively is an important component of OSA management because ES can persist despite primary OSA therapy.[1-4,24] In the current study, predominantly of men who were obese and approximately 70% of whom were using a primary OSA therapy at baseline, MWT mean sleep latency and ESS at baseline were indicative of impaired wakefulness and ES. The magnitude of improvement in participants who were randomly assigned after 4 weeks of solriamfetol treatment was notable, with MWT sleep latency more than doubling from 12 to 13 minutes to approximately 30 minutes and ESS scores decreasing from 15 to 16 to approximately 6, which is within the normative range of ≤ 10.[17,25] At the end of the stable dose phase, 14.2%

of the participants were not randomly assigned because of not meeting all three improvement criteria (ie, reporting much or very much improvement on the PGI-C with concurrent improvements on the MWT and ESS). The improvement that was observed among participants who were randomly assigned to receive solriamfetol in the randomized withdrawal phase was maintained across that phase of the study. In contrast, the MWT mean sleep latency decreased by approximately 12 minutes and ESS score increased by approximately 4.5 from week 4 to week 6 in participants switched to placebo. Neither MWT mean sleep latency nor ESS score returned to the baseline value in the placebo group, suggesting a carryover treatment effect of solriamfetol and the absence of rebound hypersomnia during this 2-week period.

Previous studies of CPAP and oral appliances reported reductions of 1.7 to 5 points on the ESS and up to a 6.5-minute improvement on MWT sleep latency.[26,27] When considering the effects of other wake-promoting agents, a meta-analysis of randomized controlled trials quantifying the efficacy of modafinil or armodafinil in sleep apnea showed that ESS scores improved by 2.2 points (95% CI, 1.5-2.9) and MWT by 3 minutes (95% CI, 2.1-3.8) relative to placebo.[28] However, the meta-analysis included studies that used 20-, 30-, and 40-minute MWT measurements, whereas the current study used a 40-minute MWT. The current trial suggests the potential for greater efficacy of solriamfetol relative to these wake-promoting agents.

Reductions in ES may be expected to translate into patient-centered benefits. In this regard, global improvements rated by the participants (PGI-C) or the physicians (CGI-C) were similarly robust, with worsening in a significantly higher percentage of participants randomly assigned to placebo relative to those who continued using solriamfetol. Additionally, the effects of solriamfetol on wakefulness and ES were paralleled by functional improvements as assessed using the FOSQ-10. These observations are comparable with what has been reported in a randomized, controlled withdrawal study of upper-airway stimulation in OSA.[29]

Solriamfetol did not result in any serious adverse events, and the six discontinuations due to adverse events all occurred during the titration phase. The safety profile was consistent with those in previous studies of solriamfetol.[12] Most of the adverse events that occurred with solriamfetol were reported during the titration phase, including headache (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), and insomnia (5.7%). There was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.

A limitation of this study is its short duration. Additionally, the inclusion of a population enriched for treatment response, which, although customary for the randomized withdrawal study design, limits characterization of solriamfetol treatment effects in individuals who did not meet response criteria for random assignment. Approximately 20% to 30% of the study population were not using a primary OSA therapy at evaluated time points, which may have induced some heterogeneity in treatment response, but subgroup analyses showed consistent effects in the adherent and nonadherent subgroups, and the inclusion of nonadherent participants in this study likely reflects the characteristics of the broad patient population with OSA who may benefit from solriamfetol in routine clinical practice.

Conclusions

This study demonstrated that solriamfetol substantially increased objective wakefulness and decreased subjective ES, with effects that were maintained in participants who continued using treatment relative to a loss of efficacy among those randomly assigned to placebo. The safety profile was consistent with those of other solriamfetol studies, and abrupt discontinuation was not associated with rebound hypersomnia or withdrawal effects.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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