Effects of Solriamfetol on Quality-of-Life Measures from a 12-Week Phase 3 Randomized Controlled Trial

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Abstract

Rationale: Excessive daytime sleepiness in patients with obstructive sleep apnea is associated with substantial burden of illness.

Objectives: To assess treatment effects of solriamfetol, a dopamine/norepinephrine reuptake inhibitor, on daily functioning, health-related quality of life, and work productivity in participants with obstructive sleep apnea and excessive daytime sleepiness as additional outcomes in a 12-week phase 3 trial (www.clinicaltrials.gov identifier NCT02348606).

Methods: Participants ($N = 476$) were randomized to solriamfetol 37.5, 75, 150, or 300 mg or to placebo. Outcome measures included the Functional Outcomes of Sleep Questionnaire short version, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, and 36-item Short Form Health Survey version 2. A mixed-effects model with repeated measures was used for comparisons with placebo.

Results: Demographics, baseline disease characteristics, daily functioning, health-related quality of life, and work productivity were similar across groups. At Week 12, increased functioning and decreased impairment were observed with solriamfetol 150 and 300 mg (mean difference from placebo [95% confidence interval]) on the basis of Functional Outcomes of Sleep Questionnaire total score (1.22 [0.57 to 1.88] and 1.47 [0.80 to 2.13], respectively), overall work impairment (−11.67 [−19.66 to −3.69] and −11.75 [−19.93 to −3.57], respectively), activity impairment (−10.42 [−16.37 to −4.47] and −10.51 [−16.59 to −4.43], respectively), physical component summary (2.07 [0.42 to 3.72] and 1.91 [0.22 to 3.59], respectively), and mental component summary (150 mg only, 2.05 [0.14 to 3.96]). Common adverse events were headache, nausea, decreased appetite, and anxiety.

Conclusions: Solriamfetol improved measures of functioning, quality of life, and work productivity in participants with obstructive sleep apnea and excessive daytime sleepiness. Safety was consistent with previous studies.

Clinical trial registered with www.clinicaltrials.gov (NCT02348606).

Keywords: JZP-110; Sunosi; excessive daytime sleepiness; obstructive sleep apnea; health-related quality of life

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Supported by Jazz Pharmaceuticals. Jazz Pharmaceuticals has worldwide development, manufacturing, and commercialization rights to solriamfetol, excluding certain jurisdictions in Asia. SK Biopharmaceuticals, the discoverer of the compound (also known as SKL-N05), maintains rights in 12 Asian markets, including Korea, China, and Japan. Jazz Pharmaceuticals provided funding to the Curry Rockefeller Group (CRG) and Peloton Advantage for writing and editorial support.

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Excessive daytime sleepiness (EDS) is common among individuals with obstructive sleep apnea (OSA) and can persist despite use of primary OSA therapy; persistent EDS is reported by an estimated 9–22% of continuous positive airway pressure (CPAP)-treated patients (1, 2). Proposed underlying pathophysiology of EDS in OSA includes sleep fragmentation due to apneic episodes and intermittent hypoxia with consequent neuronal injury to wake-promoting areas of the brain (3–5).

EDS in patients with OSA is associated with substantial burden of illness. Individuals with OSA and EDS have an increased risk of work disability compared with individuals without OSA and EDS, particularly sleeping on the job (6), and the severity of EDS correlates with decreases in work productivity (6–8). OSA and EDS are also associated with negative effects on emotional health, reduced quality of life (2, 9–11), and increased healthcare use (12). OSA is also associated with an approximately twofold increased risk of motor vehicle (13, 14) and occupational (14, 15) accidents.

Current pharmacological options for EDS in OSA include wake-promoting agents and traditional stimulants. Modafinil and armodafinil are approved for the treatment of EDS associated with narcolepsy, OSA, and shift-work disorder; however, the magnitude and duration of effect are limited in some patients (16), and rare but serious side effects (e.g., serious rash, including Stevens-Johnson syndrome) can occur, and there is a potential for reduced efficacy of oral contraceptives (17–21). Traditional stimulants such as amphetamines and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of EDS in OSA; they have high potential for abuse (drug classification schedule II) and have been associated with rebound hypersomnia (21, 22).

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (23) approved by the U.S. Food and Drug Administration (Sunosi; Jazz Pharmaceuticals) and the European Commission to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA (24, 25). The approved dose range of solriamfetol is 37.5–150 mg once daily for patients with OSA (24, 25). As previously reported in this 12-week phase 3 study of participants with OSA and associated EDS, solriamfetol demonstrated robust efficacy in improving wakefulness, as measured by the Maintenance of Wakefulness Test (MWT), and in reducing sleepiness, based on the Epworth Sleepiness Scale (ESS) (26). Significantly greater percentages of participants randomized to solriamfetol treatment also reported improvement on the Patient Global Impression of Change compared with those randomized to placebo (26). In the present study, we report how these effects of solriamfetol are associated with changes in health-related quality of life (HRQoL), daily function, and work productivity in the same population of adults with OSA and EDS.

Methods

Study Design

This was a 12-week, randomized, double-blind, placebo-controlled, multicenter, five-arm, parallel group study of the safety and efficacy of solriamfetol in the treatment of EDS in adult participants with OSA. The study was conducted at 59 clinical investigative sites in North America and the European Union—50 in the United States and Canada and 9 in France, Germany, and the Netherlands—between May 19, 2015, and December 23, 2016. The study was approved by institutional review boards or ethics committees at each site and was performed in accordance with the Declaration of Helsinki; all participants provided written informed consent (www.clinicaltrials.gov identifier NCT02348606). Full details of the study design and methods have been reported previously (26) and are summarized here.

Participants

Eligible participants were adults (18–75 yr old) diagnosed with OSA on the basis of *International Classification of Sleep Disorders, Third Edition* (ICSD-3), criteria (27). Diagnosis was determined and documented by the investigator on the basis of medical history during screening. Participants who did not have a documented diagnosis of OSA according to ICSD-3 criteria were permitted to undergo diagnostic testing for OSA during the screening period if approved by the medical monitor. All participants were required to have documented current or prior use of a primary OSA therapy (positive airway pressure, oral pressure therapy, oral appliance, upper airway stimulator, or surgical intervention), baseline ESS score greater than or equal to 10, baseline mean sleep latency shorter than 30 minutes on the 40-minute MWT, and usual nightly sleep of 6 hours or longer. Participants were excluded if they had EDS due to a cause other than OSA, had an occupation requiring nighttime or variable shift work, had a medical condition or history that could affect safety or interfere with study assessments, had recent use of any over-the-counter or prescription medications that could affect the evaluation of EDS, or refused to try a primary OSA therapy.

Treatment

Participants were randomized in a 1:1:2:2:2 ratio to receive solriamfetol 37.5, 75, 150, or 300 mg or placebo, respectively, once per day over the 12-week treatment phase. Participants randomized to the 150-mg and 300-mg doses received 75 or 150 mg, respectively, for the first 3 days. Randomization was stratified by adherence or nonadherence to primary OSA therapy at baseline. Adherence or nonadherence at study entry was determined by the investigator on the basis of clinical history and recent primary OSA therapy use based on predetermined definitions. Participants categorized as adherent included those with positive airway pressure use at least 4 h/night on at least 70% of nights or oral appliance use on at least 70% of nights. Participants with a history of a surgical intervention as primary OSA therapy were classified as adherent if the surgery was deemed to be effective in treating the airway obstruction. Nonadherence at study entry was defined as device use at a lower level than that specified above, no device use at all, or prior history of a surgical intervention deemed to be no longer effective in treating the obstruction. Participants were instructed to maintain the same primary therapy use throughout the study as at study entry. Throughout the course of the study,

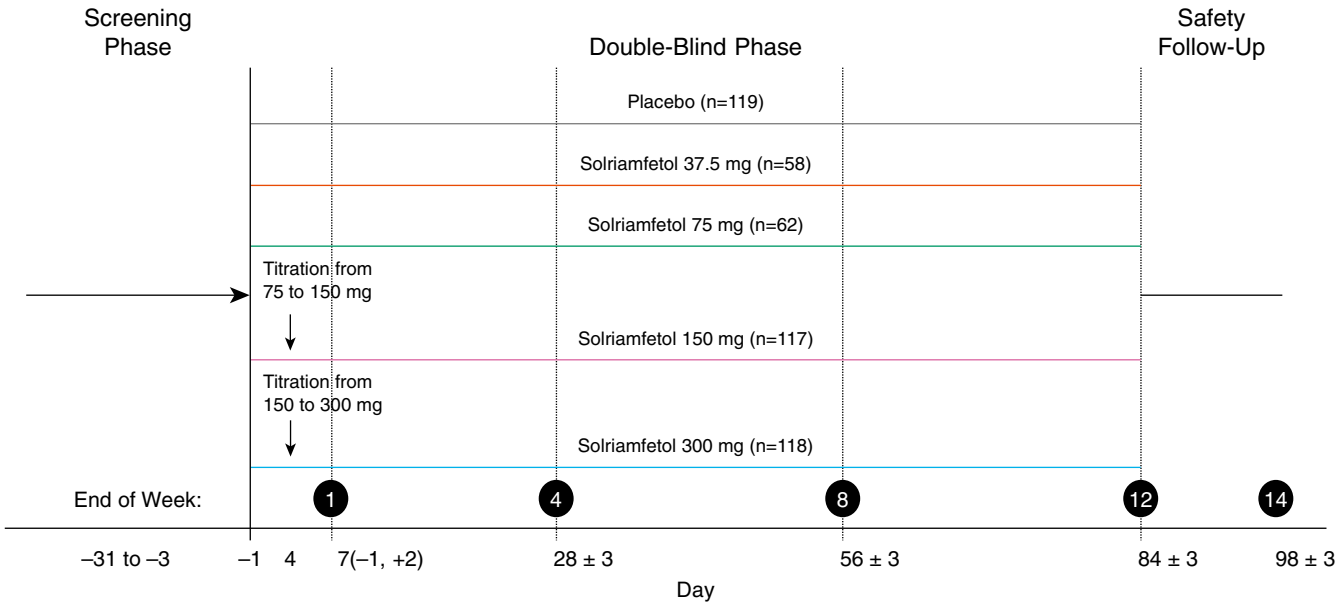

Figure 1. Study design for the phase 3, 12-week, double-blind, randomized, placebo-controlled, parallel-group study. *Note*: Numbers indicate safety population.

adherence to primary OSA therapy was assessed for those who reported using devices at baseline.

Outcomes

Efficacy and safety were assessed at the end of Weeks 1, 4, 8, and 12 (Figure 1). As reported previously (26), the coprimary efficacy endpoints were change from baseline to Week 12 in MWT sleep latency and ESS scores. MWT evaluations were performed after an overnight stay at the investigational site for nocturnal polysomnography at baseline and Weeks 1, 4, and 12.

Functional Outcomes, Quality of Life, and Work Productivity Measures

Sleep-/OSA-specific assessments. The Functional Outcomes of Sleep Questionnaire short version (FOSQ-10) is a 10-item sleepiness-specific quality-of-life questionnaire used to assess the effect of disorders associated with EDS on functional status in adults (28); higher scores represent better functioning. Change in FOSQ-10 total score was evaluated from baseline to Weeks 1, 4, 8, and 12.

The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) is a six-item self-administered questionnaire with 1-week recall that measures percentage of work time missed (absenteeism), percentage impairment while working (presenteeism), percentage overall work impairment (work impairment, absenteeism + presenteeism), and percentage activity impairment (ability to do regular daily activities other than work at a job) due to a specified health problem (OSA was the specified health problem); a negative change from baseline represents improvement (29). Work impairment was evaluated among employed participants, and activity impairment was evaluated among all participants. Change in the WPAI:SHP from baseline to Weeks 1, 4, 8, and 12 was assessed.

General assessments. The 36-item Short Form Health Survey version 2 (SF-36v2) is a multipurpose survey of 36 questions with eight functional health and well-being subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) as well as the physical component summary (PCS) and mental component summary (MCS) measures (30, 31). Changes in the subscale and summary scores were evaluated from baseline to Weeks 4, 8, and 12 (the SF-36v2 was not administered at Week 1).

The five-dimension, five-level EuroQol (EQ-5D-5L) is a standardized health outcome instrument that consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EuroQol visual analogue scale (EQ VAS) (32) and is applicable to a wide range of health conditions and treatments. Higher scores represent better quality of life. Changes in the EQ-5D-5L, EQ VAS, and EQ-5D-5L index were evaluated from baseline to Weeks 1, 4, 8, and 12.

Safety

Safety and tolerability were assessed on the basis of treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram test, physical examinations, Columbia-Suicide Severity Rating Scale (33), and laboratory tests in the safety population.

Statistical Analysis

As reported previously (26), sample size was determined on the basis of change from baseline to Week 12 on the coprimary endpoints. To detect a difference between placebo and the 150- and 300-mg groups of 5 minutes in mean sleep latency on the MWT (common standard deviation [SD] of 10 min) and 3.5 points on the ESS (common SD of 6 points), a sample size of 110 participants per group (accounting for

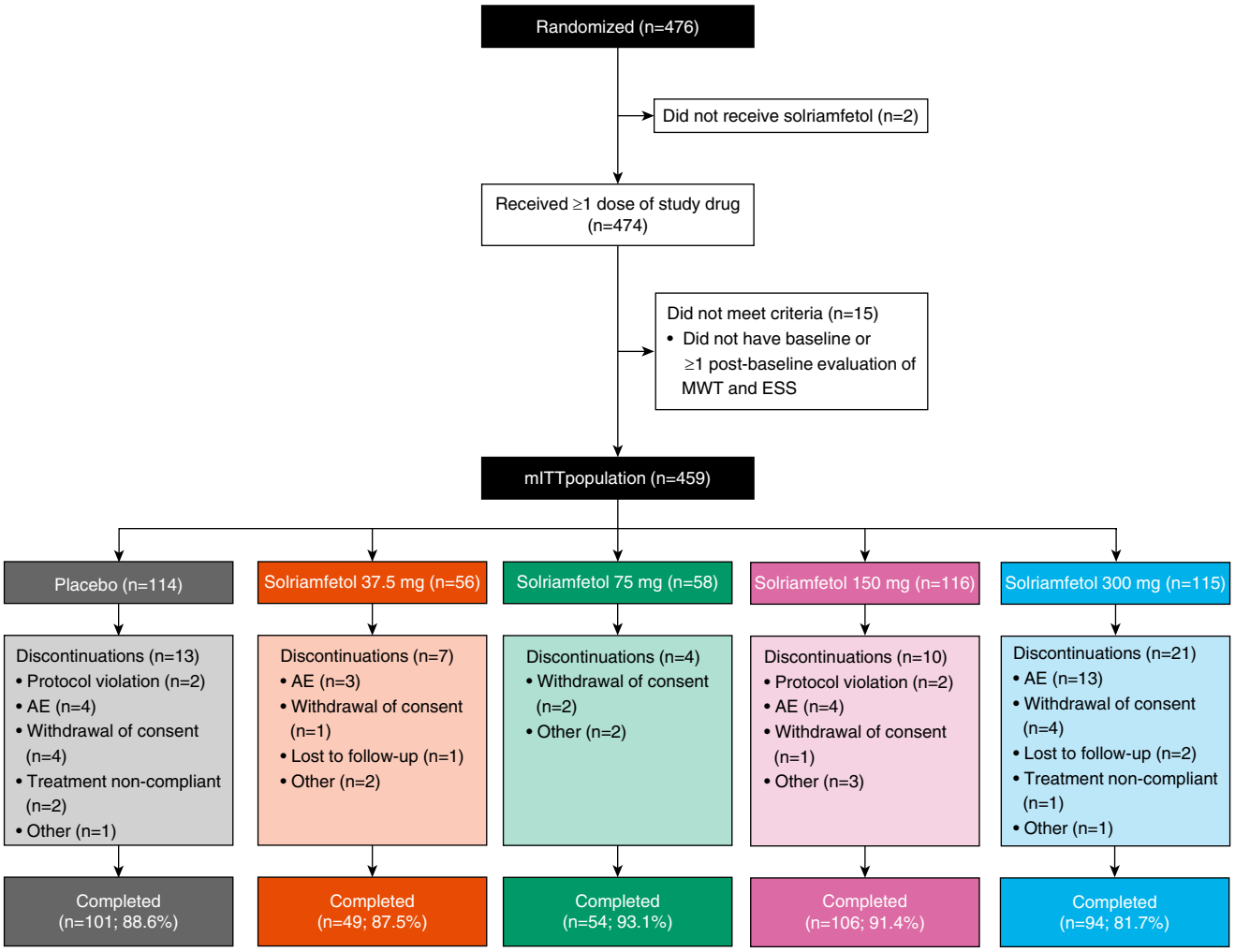

Figure 2. Participant disposition. AE = adverse event; ESS = Epworth Sleepiness Scale; mITT = modified intention to treat; MWT = Maintenance of Wakefulness Test. Adapted from Reference 26.

potential dropouts) was estimated to provide at least 90% power with a two-sided significance level of 0.05. The two lower-dose arms were not powered for statistical significance but were included to adequately characterize the minimal effective dose.

Efficacy analyses were based on the modified intention-to-treat population (mITT), defined as all participants who received at least one dose of study medication and had baseline and at least one postbaseline evaluation with the ESS or MWT. The FOSQ-10, WPAI:SHP, and SF-36v2 data were analyzed using mixed-effects model repeated measures with change from baseline as the response variable. This model included fixed effects of treatment, visit, treatment-by-visit interaction, baseline value of the efficacy endpoint, and randomization stratification factor (adherence or nonadherence to primary OSA therapy at baseline). The least squares estimates of treatment difference versus placebo and their 95% confidence intervals (CIs) are presented. EQ-5D-5L was analyzed using a chi-square test. This study was not powered for significance on the endpoints evaluated in the present study, and there were no adjustments to address the issue of multiple endpoints and dose groups for these analyses. Therefore, reported *P* values are nominal because statistical significance cannot be claimed, owing to the lack of control for multiplicity. All analyses were conducted using SAS version 9.3 or higher (SAS Institute).

Results

Participant Disposition

The study screened 984 participants and enrolled and randomized 476. Of these, 474 received at least one dose of study medication and comprised the safety population, and 459 comprised the mITT population. Approximately 97% of participants were in North America, and about 3% were in the European Union. The majority of participants randomized to receive placebo (84.9%) or a dose of solriamfetol (85.4%) completed the study. No participant withdrew from the study because of lack of efficacy. Overall, a greater number and a greater percentage of participants in the solriamfetol 300 mg group (13.6%) relative to all other

Table 1. Demographics and baseline clinical characteristics (safety population)

Variable	Placebo (*n* = 119)	Solriamfetol 37.5 mg (*n* = 58)	Solriamfetol 75 mg (*n* = 62)	Solriamfetol 150 mg (*n* = 117)	Solriamfetol 300 mg (*n* = 118)
Age, yr, mean (SD)	54.1 (11.4)	57.1 (10.2)	54.4 (11.5)	52.7 (10.6)	53.2 (10.6)
Sex, *n* (%)					
M	77 (64.7)	39 (67.2)	35 (56.5)	72 (61.5)	74 (62.7)
F	42 (35.3)	19 (32.8)	27 (43.5)	45 (38.5)	44 (37.3)
BMI, kg/m^2, mean (SD)	33.1 (5.2)	34.1 (5.3)	33.4 (5.7)	33.3 (4.8)	32.9 (5.6)
Race, *n* (%)					
White	87 (73.1)	45 (77.6)	46 (74.2)	93 (79.5)	90 (76.3)
Black or African American	26 (21.8)	10 (17.2)	14 (22.6)	18 (15.4)	21 (17.8)
Other	6 (5.0)	3 (5.2)	2 (3.2)	6 (5.1)	7 (5.9)
Mean sleep latency, min, mean (SD)*	12.4 (7.2)	13.6 (8.1)	13.1 (7.2)	12.5 (7.2)	12.0 (7.3)
ESS score, mean (SD)	15.6 (3.3)	15.1 (3.5)	14.8 (3.5)	15.1 (3.8)	15.2 (3.1)
CGI-S, *n* (%)					
1 = Normal, not at all ill	0	0	0	0	0
2 = Borderline ill	3 (2.5)	1 (1.7)	1 (1.6)	2 (1.7)	1 (0.8)
3 = Mildly ill	8 (6.7)	5 (8.6)	4 (6.5)	7 (6.0)	10 (8.5)
4 = Moderately ill	48 (40.3)	28 (48.3)	31 (50.0)	53 (45.3)	44 (37.3)
5 = Markedly ill	39 (32.8)	14 (24.1)	15 (24.2)	41 (35.0)	44 (37.3)
6 = Severely ill	15 (12.6)	9 (15.5)	7 (11.3)	14 (12.0)	17 (14.4)
7 = Among the most extremely ill	4 (3.4)	1 (1.7)	3 (4.8)	0	2 (1.7)
Missing	2 (1.7)	0	1 (1.6)	0	0
Use of primary OSA therapy, *n* (%)					
Adherent	83 (69.7)	40 (69.0)	45 (72.6)	80 (68.4)	86 (72.9)
Nonadherent	36 (30.3)	18 (31.0)	17 (27.4)	37 (31.6)	32 (27.1)
FOSQ-10 total score, mean (SD)†	13.5 (3.1)	14.1 (3.4)	13.6 (3.0)	14.1 (2.7)	14.2 (3.0)
SF-36v2, PCS, mean (SD)†‡	46.3 (7.8)	44.5 (8.4)	46.9 (8.8)	46.3 (8.5)	45.9 (8.9)
SF-36v2, MCS, mean (SD)†‡	50.7 (9.1)	50.3 (9.4)	49.8 (8.7)	50.3 (8.0)	50.3 (8.5)
WPAI:SHP§					
Percentage of work time missed, mean (SD)‖	2.6 (6.2)	3.3 (7.9)	3.1 (5.5)	3.5 (7.6)	5.0 (12.5)
Percentage impairment while working, mean (SD)¶	37.4 (26.0)	34.7 (23.6)	37.4 (26.1)	33.7 (24.6)	33.7 (26.7)
Percentage overall work impairment, mean (SD)**	47.0 (26.8)	43.2 (25.5)	43.5 (26.0)	43.1 (25.6)	45.0 (28.3)
Percentage activity impairment, mean (SD)††	44.2 (27.5)	40.9 (24.6)	42.2 (25.3)	37.8 (25.4)	41.9 (27.8)
EQ VAS total score, mean (SD)‡‡§§	76.8 (15.8)	77.0 (16.4)	77.9 (13.1)	76.8 (14.8)	76.8 (14.9)

Definition of abbreviations: BMI = body mass index; CGI-S = Clinical Global Impression-Severity; EQ VAS = EuroQol visual analogue scale; ESS = Epworth Sleepiness Scale; FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version; MCS = mental component summary; OSA = obstructive sleep apnea; PCS = physical component summary; SD = standard deviation; SF-36v2 = Short Form Health Survey version 2; WPAI:SHP = Work Productivity and Activity Impairment: Specific Health Problem.

Adapted from Reference 26.

*Sample size: placebo, *n* = 114; solriamfetol 37.5 mg, *n* = 55; 75 mg, *n* = 61; 150 mg, *n* = 116; 300 mg, *n* = 116.

†Sample size: placebo, *n* = 114; solriamfetol 37.5 mg, *n* = 56; 75 mg, *n* = 58; 150 mg, *n* = 116; 300 mg, *n* = 115.

‡Normative value for U.S. population = 50 (31).

§One-week recall. *n* values are smaller for percentage of work time missed, percentage impairment while working, and percentage overall work impairment, because they represent only those participants who were employed at the time of the study.

‖Sample size: placebo, *n* = 69; solriamfetol 37.5 mg, *n* = 30; 75 mg, *n* = 36; 150 mg, *n* = 78; 300 mg, *n* = 80.

¶Sample size: placebo, *n* = 69; solriamfetol 37.5 mg, *n* = 32; 75 mg, *n* = 35; 150 mg, *n* = 79; 300 mg, *n* = 78.

**Sample size: placebo, *n* = 68; solriamfetol 37.5 mg, *n* = 30; 75 mg, *n* = 35; 150 mg, *n* = 77; 300 mg, *n* = 78.

††Sample size: placebo, *n* = 113; solriamfetol 37.5 mg, *n* = 56; 75 mg, *n* = 58; 150 mg, *n* = 116; 300 mg, *n* = 115.

‡‡Sample size: placebo, *n* = 114; solriamfetol 37.5 mg, *n* = 56; 75 mg, *n* = 58; 150 mg, *n* = 115; 300 mg, *n* = 115.

§§EQ VAS is based on a 0–100 score, with higher scores indicating better health.

treatment groups did not complete the study because of one or more adverse events (Figure 2).

Demographics and Baseline Clinical Characteristics

Demographics and baseline clinical characteristics were similar among the treatment groups (Table 1). The majority of participants were white and male; the mean age was approximately 54 years (range, 20–75 yr), and mean body mass index was approximately 33 kg/m^2. The majority of participants were rated as moderately or markedly ill at baseline on the basis of the Clinical Global Impression–Severity and were adherent with a primary OSA therapy. ESS scores and sleep latency based on MWT were similar across all treatment groups (Table 1). Mean total sleep time based on the baseline polysomnography was 6.6 hours (SD, 0.7–0.8) for both the placebo and combined solriamfetol groups. Current use of primary OSA therapy was reported by the majority of participants: 69.7% of the placebo group and 73.5% of the solriamfetol groups. A history of a surgical intervention for OSA was reported in 17.6% and 13.5% of participants in the placebo and solriamfetol groups, respectively.

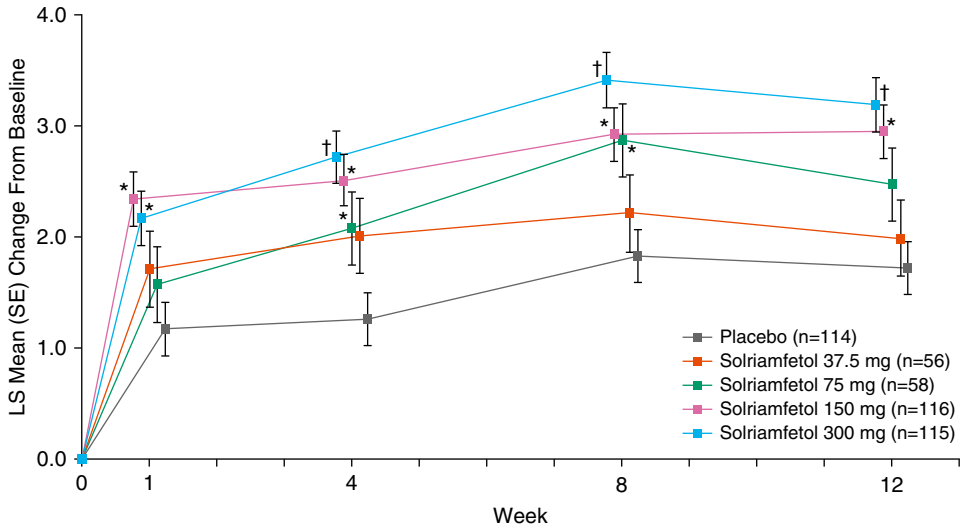

Figure 3. Change in FOSQ-10 total scores from baseline to Week 12 (mITT population). *$P < 0.05$ and †$P < 0.0001$ versus placebo. *P* values are uncontrolled for multiplicity; hence, they are nominal. Positive response from baseline denotes improvement. FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version (10-item); LS = least squares; mITT = modified intention to treat; SE = standard error.

Functional Outcomes, Quality of Life, and Work Productivity Endpoints

Sleep-/OSA-specific assessments. Baseline mean FOSQ-10 total scores ranged from 13.5 to 14.2 across treatment groups (Table 1). Increases from baseline to Week 12 in the FOSQ-10 total score were observed with solriamfetol treatment in a dose-dependent manner relative to placebo (Figure 3). At Week 12, least squares mean changes (standard error) were 1.7 (0.2) for placebo and 2.0 (0.3), 2.5 (0.3), 3.0 (0.2), and 3.2 (0.2) for solriamfetol 37.5, 75, 150, and 300 mg, respectively, with the greatest mean differences from placebo (95% CI) in the solriamfetol 150 mg and 300 mg groups (1.22 [0.57–1.88] and 1.47 [0.80–2.13], respectively).

On the WPAI:SHP (Table 1), among participants who were employed, impairment in self-reported work productivity was substantial at baseline (ranging from about 43% to 47% across treatment groups). Absenteeism was relatively low at baseline, with participants

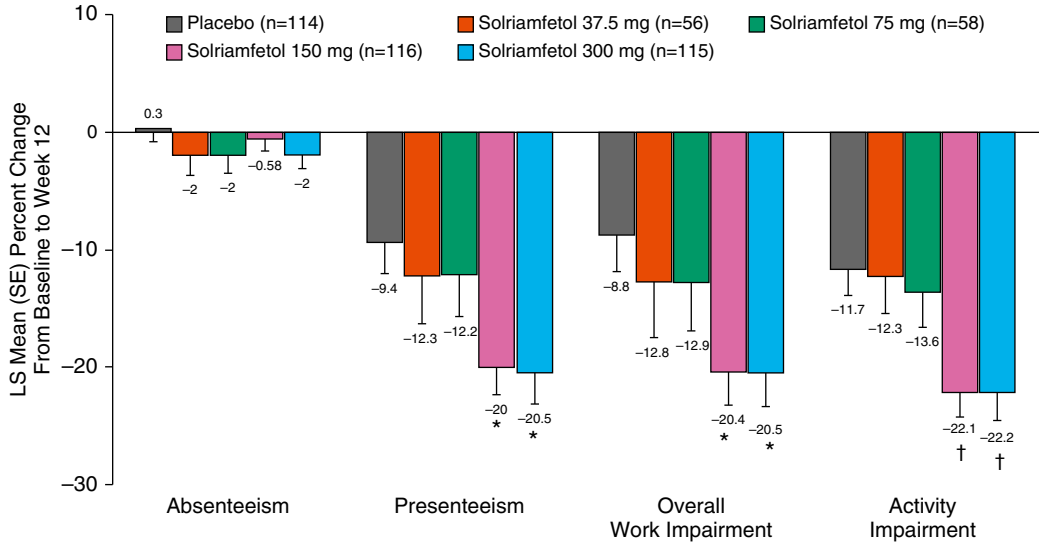

Figure 4. Change in WPAI:SHP from baseline to Week 12 (mITT population). *P* values are uncontrolled for multiplicity; hence, they are nominal. *$P < 0.05$ versus placebo. †$P < 0.001$ versus placebo. Values are for the mITT population ($n = 459$): percentage of work time missed due to OSA (absenteeism), percentage impairment while working due to OSA (presenteeism), percentage of overall work impairment due to OSA (absenteeism + presenteeism), and percentage activity impairment due to OSA. Negative response from baseline denotes improvement. LS = least squares; mITT = modified intention to treat; OSA = obstructive sleep apnea; SE = standard error; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

missing from 2.6% to 5.0% of work per week (highest in the 300-mg solriamfetol group). Activity impairment outside of work was substantial, ranging from 37.8% to 44.3% at baseline. At Week 12, dose-dependent improvements were noted for percentage impairment while working, percentage overall work impairment, and percentage activity impairment in all solriamfetol dose groups. Differences relative to placebo (least squares mean difference [95% CI]) for the 150- and 300-mg solriamfetol groups were observed for presenteeism (−10.64 [−17.55 to −3.73] and −11.16 [−18.26 to −4.05], respectively), overall work impairment (−11.67 [−19.66 to −3.69] and −11.75 [−19.93 to −3.57], respectively), and activity impairment (−10.42 [−16.37 to −4.47] and −10.51 [−16.59 to −4.43], respectively); numerical improvements at lower doses did not differ from placebo (Figure 4). No consistent changes in percentage of work time missed (absenteeism) were observed with solriamfetol treatment relative to placebo (Figure 4).

General assessments. On the SF-36v2, mean PCS and MCS scores at baseline ranged from approximately 45 to 50 across treatment groups (Table 1) (31). For the PCS score, least squares mean increases from baseline to Week 12 were observed in all solriamfetol groups (Figure 5A), with the greatest differences from placebo in the 150- and 300-mg solriamfetol treatment groups (mean difference [95% CI], 2.07 [0.42–3.72] and 1.91 [0.22–3.59], respectively). For the

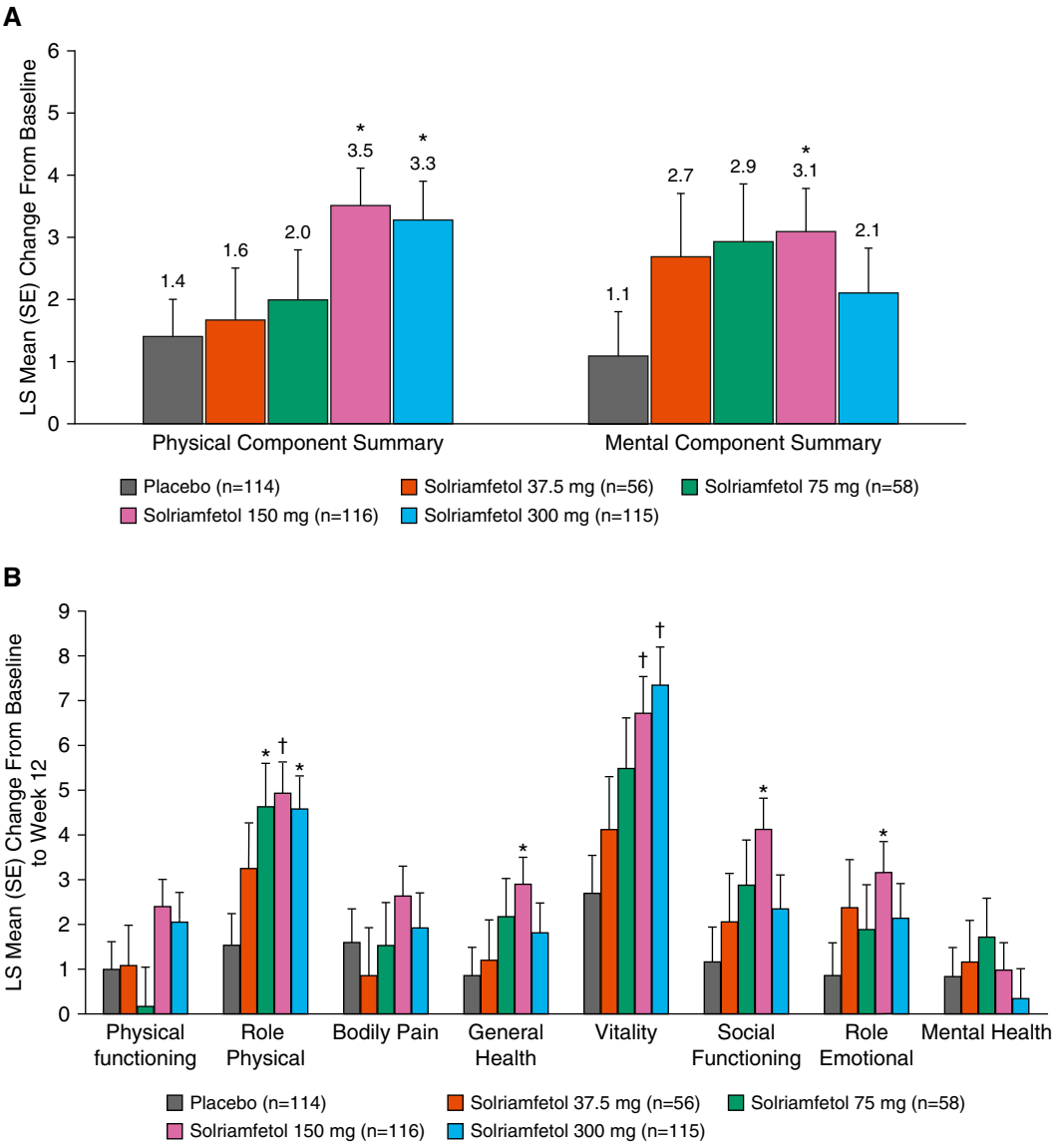

Figure 5. Change in the SF-36v2 (*A*) PCS and MCS and (*B*) subscale scores from baseline to Week 12 (mITT population). *P* values are uncontrolled for multiplicity; hence, they are nominal. *$P < 0.05$ versus placebo. †$P < 0.001$ versus placebo. Positive response from baseline denotes improvement. Values are for the mITT population ($n = 459$). LS = least squares; MCS = mental component summary; mITT = modified intention to treat; PCS = physical component summary; SE = standard error; SF-36v2 = 36-item Short Form Health Survey version 2.

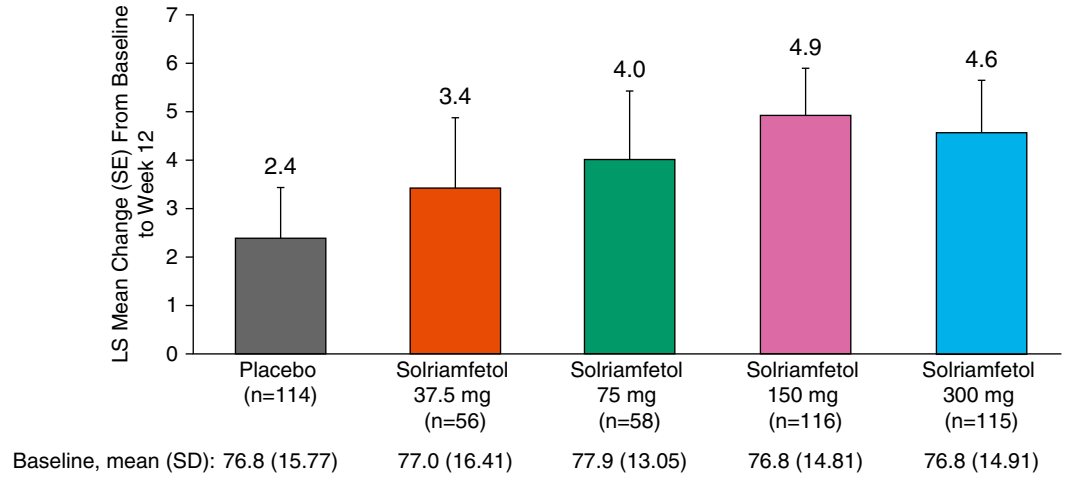

Figure 6. Change in EQ VAS from baseline to Week 12 (mITT population). Positive response denotes improvement from baseline. EQ VAS = EuroQol visual analogue scale; LS = least squares; mITT = modified intention to treat; SD = standard deviation; SE = standard error.

MCS score, least squares mean change from baseline to Week 12 reflected increases in all solriamfetol treatment groups (Figure 5A), with the greatest difference from placebo in the 150-mg group (2.05 [0.14–3.96]). For the SF-36v2 subscale scores, the greatest changes from baseline in the solriamfetol groups were observed in role physical, vitality, social functioning, and role emotional scores (Figure 5B).

For the EQ VAS, increases (improvements) from baseline to Week 12 were observed with solriamfetol treatment relative to placebo at Week 12 (Figure 6). For the EQ-5D-5L dimensions of mobility, self-care, usual activities, and pain discomfort, no meaningful changes from baseline were observed for any solriamfetol dose group relative to placebo (*see* Table E1 in the online supplement). For the EQ-5D-5L index, changes from baseline were small, and no meaningful difference was observed between the solriamfetol dose groups and placebo (*see* Table E1).

Safety

TEAEs were experienced by 241 (67.9%) of 355 participants across solriamfetol doses compared with 57 (47.9%) of 119 participants in the placebo group. The most commonly reported TEAEs (⩾5%) across all doses of solriamfetol were headache, nausea, decreased appetite, anxiety, and nasopharyngitis. Five participants, including three (0.8%) treated with solriamfetol and two (1.7%) treated with placebo, experienced seven serious TEAEs (goiter, road traffic accident, back pain, sciatica, bile duct obstruction, streptococcal endocarditis, and hyperglycemia), all of which were considered not to be related to study drug. No deaths occurred in this study. Twenty-nine participants (25 [7.0%] solriamfetol, 4 [3.4%] placebo) had a TEAE leading to premature withdrawal from the study, the most frequent being feeling jittery (1.1%) and anxiety (1.1%). One participant withdrew because of insomnia. The highest incidence of TEAEs leading to premature withdrawal occurred for those treated with solriamfetol 300 mg (12.7%) (Table 2).

Table 2. Treatment-emergent adverse events

TEAE (*n* [%])	Placebo (*n* = 119)	Solriamfetol 37.5 mg (*n* = 58)	Solriamfetol 75 mg (*n* = 62)	Solriamfetol 150 mg (*n* = 117)	Solriamfetol 300 mg (*n* = 118)	Combined Solriamfetol* (*n* = 355)
Any TEAE	57 (47.9)	37 (63.8)	30 (48.4)	83 (70.9)	91 (77.1)	241 (67.9)
Serious TEAEs	2 (1.7)	2 (3.4)	0	1 (0.9)	0	3 (0.8)
Discontinuations due to TEAEs	4 (3.4)	3 (5.2)	2 (3.2)	5 (4.3)	15 (12.7)	25 (7.0)
Most common TEAEs						
Headache	10 (8.4)	4 (6.9)	5 (8.1)	10 (8.5)	17 (14.4)	36 (10.1)
Nausea	7 (5.9)	3 (5.2)	3 (4.8)	10 (8.5)	12 (10.2)	28 (7.9)
Decreased appetite	1 (0.8)	1 (1.7)	3 (4.8)	9 (7.7)	14 (11.9)	27 (7.6)
Anxiety	0	1 (1.7)	2 (3.2)	6 (5.1)	16 (13.6)	25 (7.0)
Nasopharyngitis	8 (6.7)	2 (3.4)	1 (1.6)	7 (6.0)	8 (6.8)	18 (5.1)

Definition of abbreviation: TEAE = treatment-emergent adverse event.
Adapted from Reference 26.
*TEAEs ⩾5% in combined solriamfetol group.

Discussion

EDS is one of the most common symptoms of OSA (34) and often persists despite adherence to primary OSA therapies such as CPAP (1, 2, 9, 35). EDS confers a substantial burden of illness on patients both at work and at home, as well as a substantial burden on healthcare resources (6–8, 10–15), although it may be overlooked, and its impact may be underappreciated (36, 37). In this study, baseline assessments reflected impairment in daily functioning, HRQoL, and work productivity. Baseline FOSQ-10 total scores were lower than normal across all treatment groups (normal, ≈18) (28), indicating impairment in functioning. Among participants who were employed, self-reported overall work impairment based on the WPAI:SHP was substantial at baseline; absenteeism at baseline was relatively low, and presenteeism (impaired productivity while at work) was the main driver of overall work impairment. Baseline WPAI:SHP assessments also reflected considerable activity impairment among all study participants. On the SF-36v2, mean PCS and MCS scores at baseline were generally near or slightly lower than normative values, suggesting some impairment.

As previously reported, the primary results of this study demonstrated that solriamfetol significantly increased wakefulness as assessed by the MWT and significantly reduced EDS as assessed by the ESS, with the majority of participants reporting improvement on the Patient Global Impression of Change (26). The present analyses of secondary outcomes indicate that these effects on wakefulness and sleepiness also translated into meaningful changes in daily functioning, HRQoL, and work productivity, particularly at the 150-mg dose. Of note, least squares mean changes from baseline to Week 12 on the FOSQ-10 across solriamfetol doses ranged from 2.0 to 3.2, all of which met or exceeded the threshold for a minimally important difference (range, 1.7–2.0) (38). Furthermore, at the two highest doses (150 and 300 mg), solriamfetol improved daily functioning, HRQoL, and work productivity compared with placebo in participants with EDS associated with OSA, with similar improvement in both of the higher-dose groups. The similar effects observed for the 150- and 300-mg dose groups could be due to a ceiling effect of the therapeutic effects of solriamfetol on these outcomes in this population. This is consistent with the approved therapeutic dose range for solriamfetol (maximum approved dose is 150 mg). Differences from placebo were observed for FOSQ-10 total score; WPAI:SHP percentage impairment while at work, overall work impairment, and activity impairment outside of work; and SF-36v2 PCS score (which appeared to be driven by improvements on the role physical and vitality subscales). In addition, differences from placebo on the SF-36v2 MCS were observed with solriamfetol 150 mg. Improvements were variable on the mental, social, and emotional domains of the SF-36v2 and EQ-5D-5L component scores. There was improvement in some domains of the SF-36v2, with mean scores at Week 12 slightly higher than normative values in some cases, although few differences from placebo were observed (39). However, despite clear improvements observed on several measures of quality of life and functioning, improvement and differences from placebo were not observed on the EQ-5D-5L. Overall, in this study, disease-specific scales (FOSQ-10 and WPAI:SHP) appear to be more sensitive to detecting improvements than more general scales (SF-36v2 and EQ-5D-5L). Similar observations previously have been noted in studies of CPAP in patients with OSA and EDS (40). The limited sensitivity of the general scales is not entirely unsurprising, because these instruments are not designed to specifically assess aspects of life affected by OSA, such as those impacted by EDS (e.g., sleep propensity–related impairment) (40).

A positive impact of solriamfetol on functional and HRQoL outcomes in patients with OSA and persistent EDS despite CPAP therapy was observed in this study. A pooled analysis of two short-term studies (4–12 wk) found that treatment with modafinil (200–400 mg/d) was associated with improvements compared with placebo on FOSQ-10 total score (mean change from baseline, 1.96 vs. 1.03; $P < 0.0001$) and activity, productivity, intimacy, and vigilance subscale scores (mean changes from baseline, 0.29–0.51 with modafinil vs. 0.13–0.26 with placebo) (41). Large randomized controlled studies have not examined the effect of traditional stimulants and wake-promoting agents on measures of work productivity in adults with EDS associated with OSA.

This study included participants who were adherent and nonadherent to primary therapies for OSA, supporting the generalizability of these results to a clinical setting. However, potential differences in functioning, HRQoL, and work productivity outcomes between participants who were adherent and nonadherent were not analyzed. This study was conducted over a 12-week period; analyses of data from a study of longer-term use of solriamfetol in participants with EDS associated with OSA will be reported in a future publication.

In summary, the outcome measures evaluated in the present study largely support the previously reported robust response on primary outcome measures (i.e., increased wakefulness and reduced EDS). These data further demonstrate that solriamfetol is associated with less impairment and greater improvements in daily functioning, HRQoL, and work productivity in participants with EDS associated with OSA, with most global domains assessed improved at the 150-mg dose. These data, taken together with the robust wake-promoting effects and well-characterized safety profile of solriamfetol, support its use as a treatment option in patients with OSA and EDS. ■

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