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Authors

Weaver, Terri E
Pepin, Jean-Louis
Schwab, Richard
et al.

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SCIENTIFIC INVESTIGATIONS

Long-term effects of solriamfetol on quality of life and work productivity in participants with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea

Terri E. Weaver, PhD[1]; Jean-Louis Pepin, MD[2]; Richard Schwab, MD[3]; Colin Shapiro, PhD, MBBCh[4]; Jan Hedner, MD[5]; Mansoor Ahmed, MD[6]; Nancy Foldvary-Schaefer, DO, MS[7]; Patrick J. Strollo Jr, MD[8]; Geert Mayer, MD[9,10]; Kathleen Sarmiento, MD, MPH[11]; Michelle Baladi, PhD[12]; Morgan Bron, PharmD, MS[12]; Patricia Chandler, MD[12]; Lawrence Lee, PhD[12]; Atul Malhotra, MD[13]

[1]College of Nursing, University of Illinois Chicago, Chicago, Illinois; [2]Grenoble Alpes University and INSERM, Grenoble, France; [3]University of Pennsylvania, Philadelphia, Pennsylvania; [4]University of Toronto, Toronto, Ontario, Canada; [5]Sahlgrenska University Hospital, Gothenburg University, Gothenburg, Sweden; [6]Cleveland Sleep Research Center, Cleveland, Ohio; [7]Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio; [8]University of Pittsburgh/Veterans Administration Pittsburgh Health System, Pittsburgh, Pennsylvania; [9]Hephata Klinik, Schwalmstadt, Germany; [10]Philipps University, Marburg, Germany; [11]San Francisco Veterans Administration Health Care System, San Francisco, California; [12]Jazz Pharmaceuticals, Palo Alto, California; [13]Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego, La Jolla, California

Study Objectives: Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved in the United States and European Union for excessive daytime sleepiness in adults with narcolepsy (75–150 mg/day) or obstructive sleep apnea (OSA; 37.5–150 mg/day). In 12-week studies, solriamfetol was associated with improvements in quality of life in participants with narcolepsy or OSA. These analyses evaluated the long-term effects of solriamfetol on quality of life.

Methods: Participants with narcolepsy or OSA who completed previous solriamfetol studies were eligible. A 2-week titration was followed by a maintenance phase ≤ 50 weeks (stable doses: 75, 150, or 300 mg/day). Quality of life assessments included 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. Mean (standard deviation) changes from baseline to end of study were evaluated. Data were summarized descriptively. Adverse events were assessed.

Results: Safety population comprised 643 participants (417 OSA, 226 narcolepsy). Solriamfetol improved Functional Outcomes of Sleep Questionnaire short version Total scores (mean change [standard deviation], 3.7 [3.0]) and 36-Item Short Form Health Survey version 2 Physical and Mental Component Summary scores (3.1 [6.9] and 4.3 [8.4], respectively); improvements were sustained throughout treatment. On Work Productivity and Activity Impairment Questionnaire: Specific Health Problem, solriamfetol reduced (improved) % presenteeism, % overall work impairment, and % activity impairment by a minimum of 25%. Common adverse events (≥ 5%): headache, nausea, nasopharyngitis, insomnia, dry mouth, anxiety, decreased appetite, and upper respiratory tract infection.

Conclusions: Long-term solriamfetol treatment was associated with clinically meaningful, sustained improvements in functional status, work productivity, and quality of life for up to 52 weeks. Adverse events were similar between narcolepsy and OSA.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: A Long-Term Safety Study of JZP-110 in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or OSA; Identifier: NCT02348632; URL: https://clinicaltrials.gov/ct2/show/NCT02348632

Keywords: JZP-110, Sunosi, HRQoL, sleep disorders, OSA, functional status, work productivity, narcolepsy, quality of life

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Short- and long-term treatment with solriamfetol have been shown to improve excessive daytime sleepiness in participants with narcolepsy or obstructive sleep apnea. In addition, data have demonstrated that short-term treatment has been associated with improvements in quality of life. The current study evaluated whether improvements in quality of life are sustained during long-term treatment.

Study Impact: Long-term solriamfetol treatment was associated with sustained improvements in functional status, work productivity, and quality of life for up to 52 weeks. These findings demonstrate the clinical relevance of the sustained efficacy findings observed during long-term solriamfetol treatment.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a prominent symptom of narcolepsy and obstructive sleep apnea (OSA). EDS affects all patients with narcolepsy, and population-based studies estimate that 9–22% of patients with OSA continue to experience EDS despite treatment with continuous positive airway pressure (CPAP).[1,2] EDS has been shown to have many adverse consequences in participants with narcolepsy and OSA, including impairments in daytime functioning, reduced quality of life (QoL), and increased risk of workplace and driving accidents.[3–9] Furthermore, a recent study demonstrated a relationship between severity of EDS (as measured by the Epworth Sleepiness Scale) and degree of impairment in QoL and functioning such that increasing severity of EDS is associated with a greater degree of impairment.[10]

Solriamfetol (Sunosi; Jazz Pharmaceuticals, Palo Alto, CA) is a dopamine and norepinephrine reuptake inhibitor approved in the United States and the European Union to improve wakefulness in adults with EDS associated with narcolepsy (75 to 150 mg/day) or OSA (37.5 to 150 mg/day).[11,12] Solriamfetol has been shown to have short-term and long-term efficacy in the treatment of EDS in patients with narcolepsy or OSA.[13–16] In two 12-week, phase 3 studies, solriamfetol was also associated with improvements in functioning, work productivity, and health-related QoL (HRQoL) in participants with EDS associated with narcolepsy or OSA[6,17]; however, it is unknown whether these improvements are sustained with long-term treatment. The most common treatment-emergent adverse events (TEAEs) in solriamfetol-treated participants with narcolepsy or OSA in clinical trials were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, insomnia, and anxiety.[13,14,16]

The current analyses examined whether long-term treatment with solriamfetol had sustained benefits with regard to functional status, work/activity impairment, and HRQoL. Adverse events (AEs) were also evaluated in this long-term study.

METHODS

Study design

The full methods of this study have been reported previously[16] and are briefly summarized here. This was a long-term (up to 52 weeks), open-label extension phase 3 clinical trial that evaluated the efficacy and safety of solriamfetol for the treatment of EDS in adult participants with narcolepsy or OSA. The study was conducted at 79 clinical investigative sites in North America (63 sites) and Europe (16 sites) between May 26, 2015, and December 8, 2017. The study was approved by institutional review boards or ethics committees at each institution and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. Results of the primary analyses of this study have been reported previously[16]; results of the secondary analyses are presented below.

Participants

Participants with narcolepsy or OSA who had previously completed a phase 2 or 3 clinical trial of solriamfetol (including NCT02806895/EudraCT 2015-003930-28 and NCT02806908/EudraCT 2015-003931-36 and several trials with published results[13–15,18,19]) were eligible for enrollment in the open-label extension study. Due to differences in time between prior study completion and enrollment in the current study, there were 2 groups. Group A was enrolled in the open-label extension study immediately after completion of 12-week phase 3 studies. Participants in Group B historically completed phase 2 studies or the 6-week phase 3 study and were subsequently enrolled in the open-label extension study (the time between studies could range from 0 to 48 months, depending on the timing of the completion of the parent study).

In addition to having met the inclusion criteria and completing a previous clinical trial of solriamfetol, participants also had a usual nightly total sleep time of at least 6 hours, body mass index between 18 and 45 kg/m^2, and were, in the opinion of the investigator, able to take solriamfetol for 40 (Group A) or 52 weeks (Group B). Key exclusion criteria included usual bedtime later than 1AM, nighttime or variable shiftwork, or having experienced any serious AE related to solriamfetol or any AE in a previous study that may prevent safe participation in the current study. Use of prescription or over-the-counter medications that could impact the evaluation of EDS was prohibited during the study.

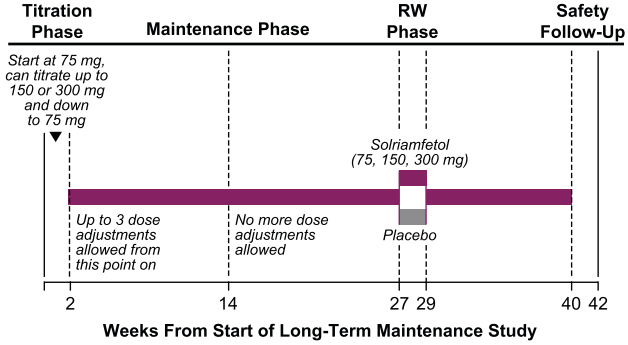
Treatment

Open-label solriamfetol treatment for all participants in both Group A and Group B, regardless of treatment assignment in the parent study, was initiated at 75 mg during a 2-week titration phase, during which the dose could be titrated up 1 dose level every 3 days (to 150 mg and then a maximum dose of 300 mg) (**Figure 1**).[16] Investigators were instructed to titrate solriamfetol to the maximum dose tolerated by each participant to maximize efficacy based on their clinical judgment of patients' self-reported response. No objective measurements were used to determine dosage levels. During the titration phase, down-titration was permitted at any time for safety reasons. After the titration phase, up to 3 dose adjustments were allowed within the first 12 weeks of the maintenance phase. Participants whose doses could not be successfully adjusted were discontinued from the study. The titration phase was followed by an open-label maintenance phase (75, 150, or 300 mg), with a total study duration of 40 weeks for Group A and 52 weeks for Group B. After approximately 6 months of open-label treatment with solriamfetol, a subgroup (approximately 300 participants from Groups A and B were planned; there were no randomization criteria with respect to group) entered a 2-week placebo-controlled, randomized withdrawal phase (**Figure 1**), and the maintenance phase was resumed after the completion of the randomized withdrawal phase.

Functional outcomes, QoL, and work productivity measures

The impact of EDS on functional status, work/activity impairment related to narcolepsy or OSA, and general HRQoL was assessed with the Functional Outcomes of Sleep Questionnaire

Figure 1—Study design.[a]



[a]Study design for Group A only; Group B was similar except total duration was 52 weeks. Adapted from Malhotra et al.[16] RW = randomized withdrawal.

short version (FOSQ-10), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP; specified as narcolepsy or OSA), and 36-item Short Form Health Survey Version 2 (SF-36v2), respectively. These assessments were administered at weeks 14, 27, 29 (FOSQ-10 only), and 40 for participants in Group A and at weeks 14, 26, 28 (FOSQ-10 only), 39, and 52 for participants in Group B, and at any early termination visits that occurred after week 2. Changes in FOSQ-10, WPAI:SHP, and SF-36v2 endpoints were assessed during the open-label phase as changes from baseline of the parent study (Group A) or baseline of the current study (Group B) to the end of the open-label phase; baseline of the parent study was used for Group A, as this represents the true pretreatment baseline for these participants. Changes in FOSQ-10 from the beginning to the end of the randomized withdrawal phase (Groups A and B combined) were also assessed; other outcomes were not assessed for the randomized withdrawal phase.

The FOSQ-10 is a 10-item questionnaire that assesses how daytime sleepiness affects daily functioning,[20] with higher scores representing better functioning, and a total score < 17.9 indicating abnormal functioning.[20,21]

The WPAI:SHP is a 6-item questionnaire that estimates how a specific health problem has impacted work productivity and activity impairment outside of work over the previous week.[22] Specifically, percent work time missed (absenteeism), percent impairment while working (presenteeism), percent overall work impairment (absenteeism + presenteeism), and percent activity impairment (ability to do regular daily activities other than work at a job) due to a specific health problem (narcolepsy or OSA) were analyzed. Work impairment was evaluated in employed participants, whereas activity impairment was evaluated in all participants. Normative values have not been established for the WPAI:SHP in narcolepsy or OSA.

The SF-36v2 is a 36-question health survey that estimates a functional health status profile with Physical Component Summary and Mental Component Summary scores, as well as 8 subscales (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health).[23,24] Each subscale has a normative mean value of 50 with a standard deviation of 10 in the US population.[25]

Safety

Safety and tolerability of solriamfetol were evaluated across the entire study and based on TEAEs.

Statistical analysis

All data during the open-label phase were analyzed for the safety population, defined as participants who received at least 1 dose of solriamfetol. Changes in efficacy endpoints during the open-label phase were analyzed with descriptive statistics; no formal statistical testing, including missing data imputation, was performed. Summary statistics were reported for the overall study population and by indication (narcolepsy or OSA) for the combined solriamfetol dose group. For the purposes of this report, results reported for the assessments in the open-label period focus on Group A, which comprised the largest cohort of participants with long-term exposure to solriamfetol (data for Group B are provided in supplemental figures).

Changes in FOSQ-10 total score from beginning to end of the randomized withdrawal phase were analyzed for the modified intent-to-treat population (ie, all participants who were randomized in the randomized withdrawal phase, took at least 1 dose of study treatment in the randomized withdrawal phase, and had evaluable data at the end of the randomized withdrawal phase), overall and by indication, using analysis of covariance models; because no adjustments for multiplicity were used, *P* values are nominal. Results from the randomized withdrawal phase include data from participants in Groups A and B combined.

Baseline patient demographics, baseline clinical characteristics, and adverse events were summarized descriptively and are reported for the full safety population (Groups A and B combined).

RESULTS

Participant population

A total of 651 participants were screened for eligibility (**Figure 2**). Of these, 643 participants, 417 (64.9%) with OSA and 226 (35.1%) with narcolepsy (114/226 [50.4%] with cataplexy) were included in the safety population. Groups A and B consisted of 519 (80.7%) and 124 (19.3%) participants, respectively. A total of 458 participants (overall, 71.2%; OSA, 73.9%; narcolepsy, 66.4%) completed the study, with the most frequently reported reasons for discontinuation being AEs (narcolepsy, n = 23; OSA, n = 38) and lack of efficacy (narcolepsy, n = 39; OSA, n = 15) (**Figure 2**).[16]

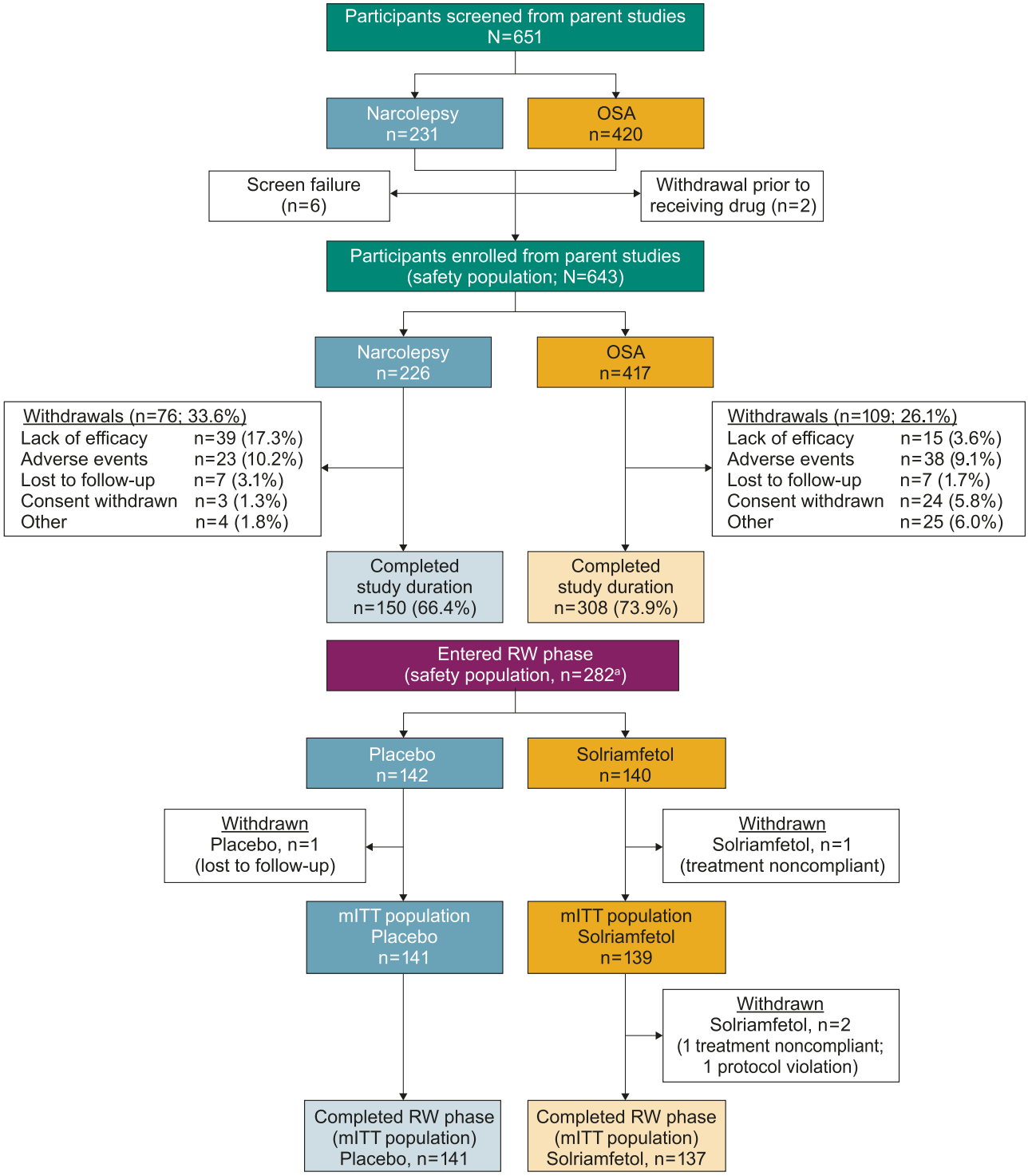
Participants with OSA were, on average, older, predominately male, and had a higher body mass index compared with participants with narcolepsy (**Table 1**). In general, participants with narcolepsy had greater impairments in functional status and work productivity/activity impairment at baseline compared with participants with OSA (**Table 2**).

Functional outcomes, QoL, and work productivity endpoints

For Group A, mean (standard deviation [SD]) FOSQ-10 total scores at parent study baseline were 13.1 (3.2), 11.6 (3.0), and 13.9 (3.0) in the overall, narcolepsy, and OSA populations, respectively. Mean (SD) changes from baseline of the parent study to week 40 in FOSQ-10 total scores were 3.7 (3.0), 3.7 (3.2), and 3.8 (2.9) for the overall, narcolepsy, and OSA populations, respectively (**Figure 3**). Improvements were sustained for the duration of solriamfetol treatment. Group B showed similar results (**Figure S1A** in the supplemental material).

At the beginning of the randomized withdrawal phase (**Figure 4**), mean (SD) FOSQ-10 total scores were 17.1 (2.7) and 17.4 (2.8) for the placebo and solriamfetol groups, respectively. Participants randomized to placebo showed greater worsening on the FOSQ-10 (mean [SD] change: −2.5 [3.14]) compared with participants who remained on solriamfetol (mean [SD] change: −0.82 [2.09]; least-squares mean difference [95% confidence interval]: 1.7 [1.11, 2.37]; $P < .0001$). These

Figure 2—Participant disposition.



[a]A total of 226 from Group A, 56 from Group B. Adapted from Malhotra et al.[16] mITT = modified intent-to-treat, OSA = obstructive sleep apnea, RW = randomized withdrawal.

Table 1—Baseline demographic characteristics of the safety population.[a]

Variable	Overall (N = 643)	Narcolepsy (n = 226)	OSA (n = 417)
Age, years, mean (SD)	49.3 (14.2)	38.7 (13.5)	55.1 (10.7)
Male, n (%)	337 (52.4)	80 (35.4)	257 (61.6)
Race, n (%)			
White	506 (78.7)	181 (80.1)	325 (77.9)
Black	109 (17.0)	33 (14.6)	76 (18.2)
Asian	15 (2.3)	4 (1.8)	11 (2.6)
Native Hawaiian/Other Pacific Islander	3 (0.5)	1 (0.4)	2 (0.5)
American Indian/Alaska Native	2 (0.3)	1 (0.4)	1 (0.2)
BMI, kg/m^2, mean (SD)	31.7 (5.9)	28.3 (5.8)	33.5 (5.1)
Medical history, n (%)			
Hypertension	242 (37.6)	39 (17.3)	203 (48.7)
Hyperlipidemia	98 (15.2)	8 (3.5)	90 (21.6)
Type 2 diabetes	90 (14.0)	7 (3.1)	83 (19.9)

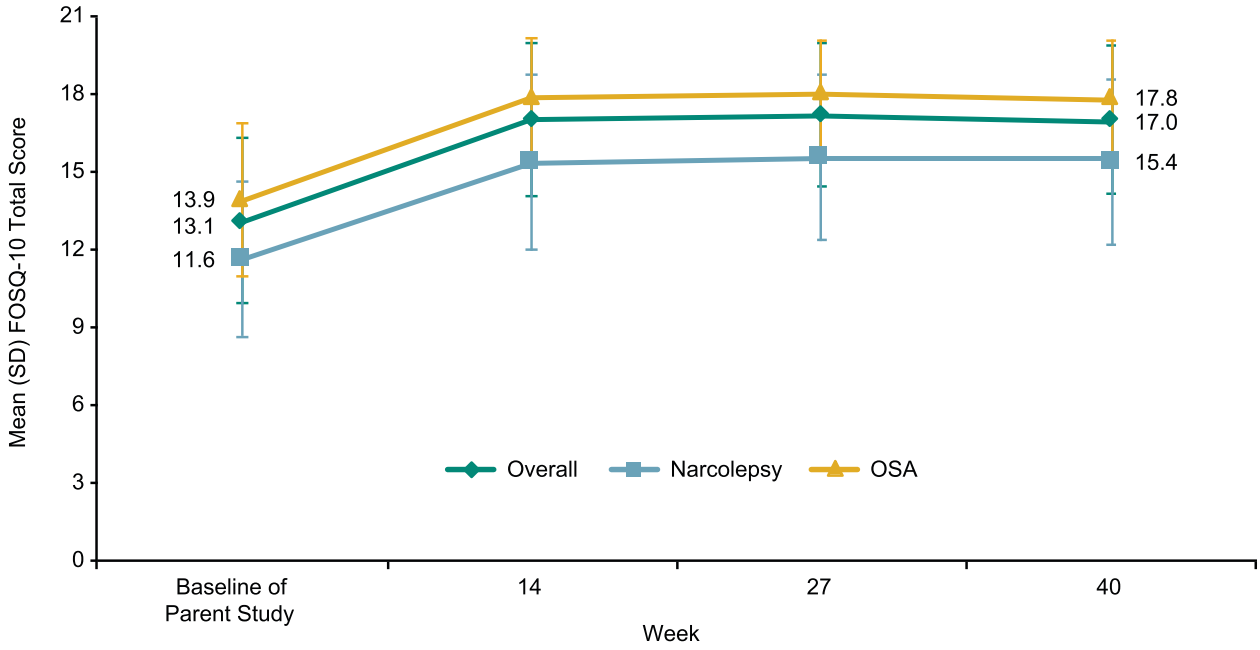
[a]Groups A and B combined. BMI = body mass index, OSA = obstructive sleep apnea, SD = standard deviation.

Table 2—Clinical characteristics of the safety population.

Variable	Overall (N = 643)	Narcolepsy (n = 226)	OSA (n = 417)
Baseline FOSQ-10 total score,[a] mean (SD)	n = 518	n = 185	n = 333
	13.1 (3.2)	11.6 (3.0)	13.9 (3.0)
Baseline WPAI:SHP,[a] mean (SD)			
% Work time missed (absenteeism)	n = 332	n = 111	n = 221
	5.3 (11.8)	9.8 (16.3)	3.1 (7.9)
% Impairment while working (presenteeism)	n = 326	n = 108	n = 218
	43.5 (26.6)	58.9 (21.1)	35.9 (25.7)
% Overall work impairment	n = 324	n = 107	n = 217
	52.6 (26.5)	67.5 (19.0)	45.2 (26.5)
% Activity impairment	n = 516	n = 184	n = 332
	49.6 (26.8)	64.1 (22.4)	41.6 (25.7)
Baseline SF-36v2,[a] mean (SD)	n = 519	n = 186	n = 333
Physical component score	46.2 (8.5)	46.2 (8.7)	46.1 (8.4)
Mental component score	48.6 (9.2)	45.4 (9.5)	50.4 (8.5)
Role physical	42.8 (10.6)	39.5 (11.3)	44.7 (9.6)
General health	49.1 (9.3)	48.7 (9.6)	49.4 (9.2)
Vitality	42.8 (9.5)	39.7 (9.3)	44.6 (9.2)
Physical functioning	48.4 (8.1)	49.4 (8.0)	47.9 (8.1)
Bodily pain	49.2 (9.7)	50.3 (10.2)	48.5 (9.3)
Role emotional	48.8 (9.8)	47.4 (10.4)	49.5 (9.4)
Mental health	51.2 (7.9)	49.5 (8.7)	52.1 (7.3)
Social functioning	46.1 (10.4)	41.6 (11.5)	48.6 (8.9)

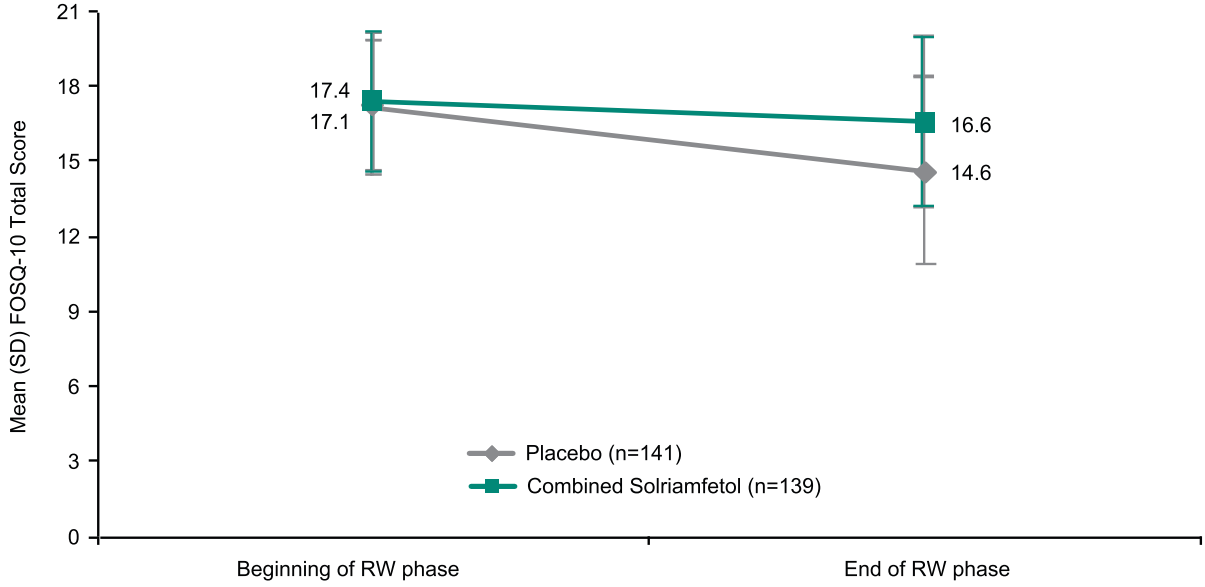
[a]Baseline in the parent study. FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, OSA = obstructive sleep apnea, SD = standard deviation, SF-36v2 = Short Form Health Survey Version 2, WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Figure 3—Change in FOSQ-10 Total score during the open-label phase.[a]



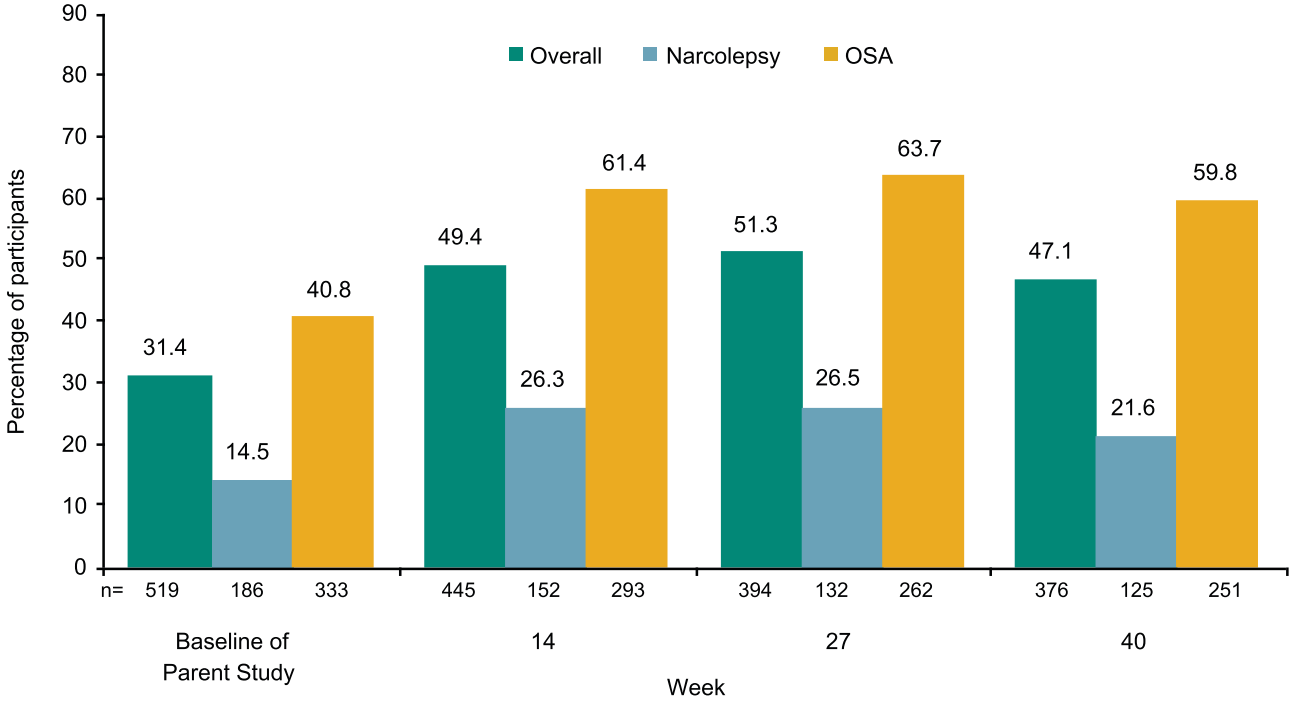
[a]Group A only. A positive change from baseline indicates improvement. FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, OSA = obstructive sleep apnea, SD = standard deviation.

Figure 4—Change in FOSQ-10 total score during the randomized withdrawal phase.[a]



[a]Groups A and B combined. The end of the RW phase was scheduled at week 29 for Group A and week 28 for Group B. FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, OSA = obstructive sleep apnea, RW = randomized withdrawal, SD = standard deviation.

Figure 5—Percentage of participants with FOSQ-10 total scores in normal range (≥ 17.9).[a]



[a]Group A only. Percentages are based on the number of participants with no missing data at a specific visit. FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, OSA = obstructive sleep apnea.

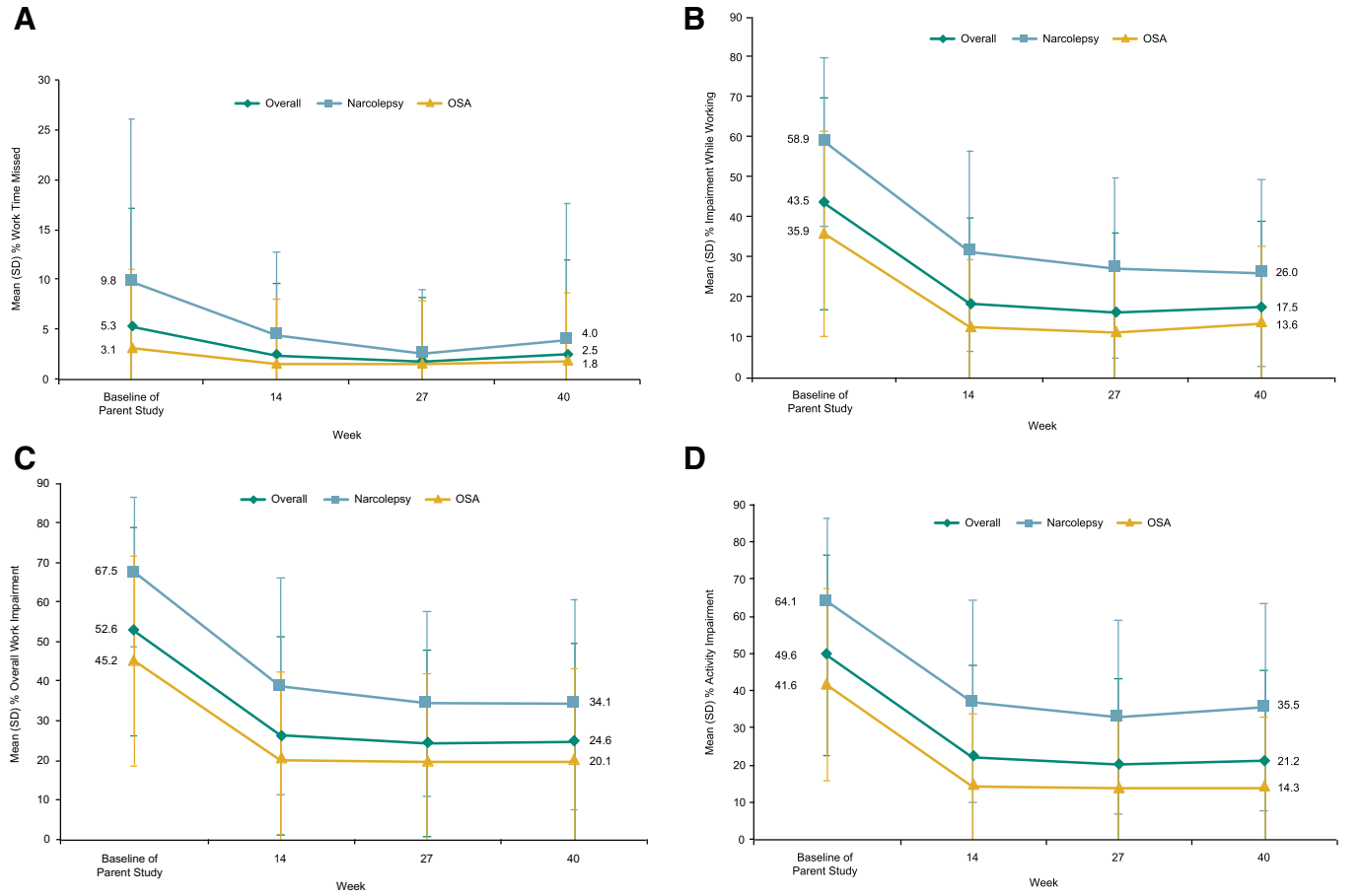
effects were similar in the subgroups of participants with narcolepsy (mean [SD] changes: placebo, −2.92 [2.8]; solriamfetol, −0.78 [1.6] and OSA (mean [SD] changes: placebo, −2.4 [3.3]; solriamfetol, −0.83 [2.3]).

For Group A, at week 40, FOSQ-10 scores ≥ 17.9 (in the normal range) were reported for 47.1%, 21.6%, and 59.8% of participants in the overall, narcolepsy, and OSA populations, respectively (**Figure 5**). Data for Group B at week 52 are shown in **Figure S1B**.

Approximately 63% of participants in Group A and 52% of participants in Group B were employed based on the number of participants who provided responses to the WPAI:SHP work-related items. At baseline, rates of absenteeism were low overall and higher among participants with narcolepsy compared with participants with OSA (**Figure 6A**). Specifically, at baseline, participants with narcolepsy reported missing 9.8% of work hours per week, whereas participants with OSA reported missing 3.1%. Likely due to the higher rate of absenteeism at baseline in participants with narcolepsy, a reduction (improvement) in the percentage of absenteeism during solriamfetol treatment was more apparent in the population with narcolepsy than those with OSA. Participants with narcolepsy and those with OSA reported high levels of impairment at baseline based on mean percent impairment while working (presenteeism), mean percent overall work impairment, and mean percent activity impairment (**Figure 6B–D**). In Group A (overall population), the percentage of presenteeism, overall work impairment, and activity impairment during solriamfetol treatment were reduced (improved) by ≥ 25% from baseline of the parent study; these improvements were maintained for the duration of treatment and generally greater in the narcolepsy population (**Figure 6B–D**). Specifically, from baseline of the parent study to week 40, mean percent presenteeism improved [mean change (SD)] by 25.2% (26.3), 29.5% (25.5), and 23.3% (26.6) for the overall, narcolepsy, and OSA populations, respectively. Mean percent overall work impairment improved by 26.1% (28.6), 29.5% (28.8), and 24.6% (28.4), respectively. Mean percent activity impairment improved by 26.7% (28.0), 26.7% (27.9), and 26.8% (28.0), respectively. Group B showed similar results (**Figure S2A–D** in the supplemental material).

For the SF-36v2, baseline mean (SD) Physical Component Summary scores for Group A were 46.2 (8.5), 46.2 (8.7), and 46.2 (8.5) for the overall, narcolepsy, and OSA populations, respectively. Baseline mean (SD) Mental Component Summary scores were 48.6 (9.2), 45.4 (9.5), and 50.4 (8.5), respectively. Physical Component Summary and Mental Component Summary scores increased (improved) with solriamfetol treatment, and these increases were maintained for the duration of treatment (**Figure 7A**). There was high variability between participants on the individual subscale scores of the SF-36v2 (**Figure 7B**); the largest magnitude of change was observed in the vitality domain for both participants with narcolepsy and OSA (**Figure 7C**).

Figure 6—Change in EDS-related work/activity impairment on the WPAI:SHP.[a]



(A) Absenteeism (work time missed). **(B)** Presenteeism (impairment while working). **(C)** Overall work impairment. **(D)** Activity impairment. [a]Group A only. [b]Regular daily activities other than work at a job. A negative change from baseline indicates improvement. EDS = excessive daytime sleepiness, OSA = obstructive sleep apnea, SD = standard deviation, WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Group B showed similar results on SF-36v2 measures (**Figure S3A-C** in the supplemental material).

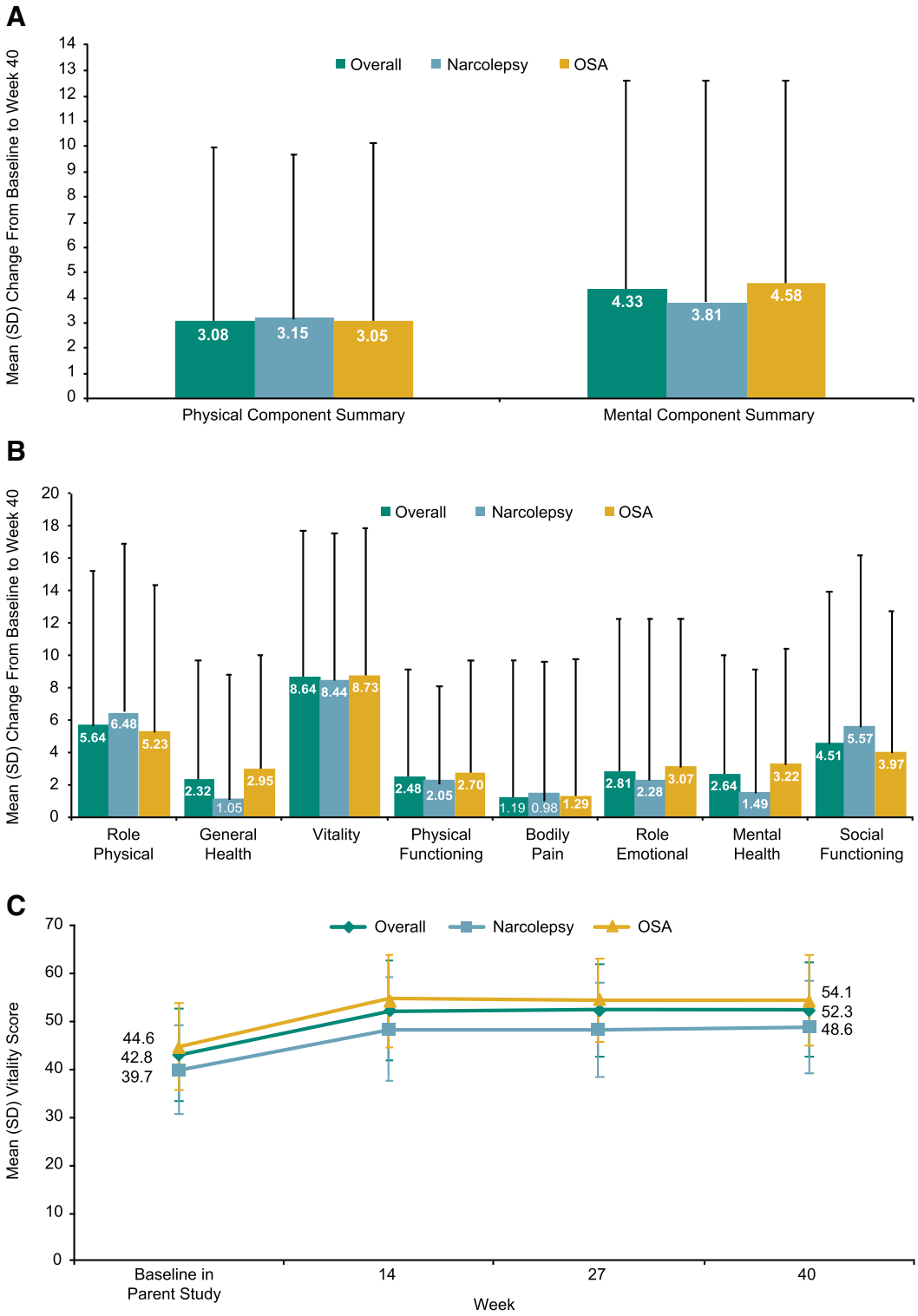
Safety

TEAEs were experienced by 169/226 (74.8%) participants with narcolepsy and 313/417 (75.1%) participants with OSA. The most commonly reported TEAEs (≥ 5%) were headache, nausea, nasopharyngitis, insomnia, dry mouth, and anxiety in participants with narcolepsy and OSA and decreased appetite in participants with narcolepsy and upper respiratory tract infection in participants with OSA (**Table 3**). Serious TEAEs were reported in 27 (4.2%) participants, 6 with narcolepsy (2.7%) and 21 with OSA (5.0%). Five participants, 1 with narcolepsy and 4 with OSA, had a serious TEAE that was considered related to the study drug by the investigator. These events included cerebrovascular accident, stillbirth, atrial fibrillation, spontaneous abortion, and retinal vein occlusion. There was 1 death due to sepsis: a 70-year-old immunosuppressed male with OSA on solriamfetol 300 mg who had a history of diabetes mellitus, rheumatoid arthritis, pulmonary fibrosis, coronary artery disease, and bipolar disorder. The death was considered unrelated to the study drug by the investigator. A total of 59 (9.2%) participants, 23 (10.2%) with narcolepsy and 36 (8.6%) with OSA, had a TEAE leading to discontinuation from the study.

DISCUSSION

Baseline assessments from the current study demonstrated that narcolepsy and OSA were associated with impairments in daily functioning and work/activity in this study population. Specifically, baseline FOSQ-10 total scores were lower than normative values (normal, 17.9–20.0)[20] for both participants with narcolepsy and OSA, suggesting difficulties with productivity, activity level, attention, social outcomes, and relationships due to EDS. Self-reported impairment in completing activities at work and outside of work may be considered in the context of data from matched controls for patients with narcolepsy or OSA reported

Figure 7—Change in general HRQoL scores on the SF-36v2.[a]



(A) Physical and Mental Component Summary scores. **(B)** Subscale scores. **(C)** Vitality domain. [a]Group A only. A positive change from baseline indicates improvement. HRQoL = health-related quality of life, OSA = obstructive sleep apnea, SD = standard deviation, SF-36v2 = Short Form Health Survey version 2.

Table 3—TEAEs across the entire study.[16]

TEAEs	Number (%) of Participants in Combined Solriamfetol Groups		
	Overall (N = 643)	Narcolepsy (n = 226)	OSA (n = 417)
At least 1 TEAE	482 (75.0)	169 (74.8)	313 (75.1)
Serious TEAE	27 (4.2)	6 (2.7)	21 (5.0)
TEAEs leading to discontinuation	59 (9.2)	23 (10.2)	36 (8.6)
Death	1 (0.2)[a]	0	1 (0.2)
Most common TEAEs[b]			
Headache	71 (11.0)	31 (13.7)	40 (9.6)
Nausea	57 (8.9)	26 (11.5)	31 (7.4)
Nasopharyngitis	54 (8.4)	19 (8.4)	35 (8.4)
Insomnia	51 (7.9)	16 (7.1)	35 (8.4)
Dry mouth	47 (7.3)	14 (6.2)	33 (7.9)
Anxiety	46 (7.2)	21 (9.3)	25 (6.0)
Decreased appetite	32 (5.0)	18 (8.0)	14 (3.4)
Upper respiratory tract infection	32 (5.0)	10 (4.4)	22 (5.3)

[a]Due to sepsis. [b]≥5% in combined solriamfetol groups for any indication. OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event.

in population-based studies. For instance, in matched controls without narcolepsy from a population-based study, rates of presenteeism, overall work impairment, and activity impairment were estimated to be 22%, 25%, and 34%, respectively.[26] In the current study, participants with narcolepsy reported rates of presenteeism, overall work impairment, and activity impairment of 59%, 68%, and 64%, respectively, at baseline. In matched controls without OSA from a population-based study, rates of presenteeism, overall work impairment, and activity impairment were 15%, 17%, and 20%, respectively.[27] In the current study, participants with OSA reported rates of presenteeism, overall work impairment, and activity impairment of 36%, 45%, and 42%, respectively, at baseline. These data support the high level of functional impairment associated with EDS in these 2 conditions.

The current analyses demonstrated sustained benefits in functional status, HRQoL, and work/activity impairment with long-term solriamfetol treatment for up to 52 weeks, as assessed by the FOSQ-10, SF-36v2, and WPAI:SHP. Notably, mean improvements in functional status on the FOSQ-10 exceeded the threshold for a minimally important difference (change of 1.7–2.0[28]), suggesting clinically meaningful improvements, and were sustained for the duration of solriamfetol treatment for some participants. Results during the randomized withdrawal phase also demonstrated long-term maintenance of efficacy of solriamfetol on the FOSQ-10 under double-blind, placebo-controlled conditions. On the SF-36v2 scales for role physical, vitality, and social functioning, mean changes from baseline also exceeded the threshold for minimal clinically important differences (2 points for role physical and 3 points for vitality and social functioning[29]), reflecting clinically meaningful improvement in these domains. In addition, solriamfetol led to sustained improvements in work and activity impairment as assessed by the WPAI:SHP. In addition to the observation of sustained improvements during the study, it is important to note that mean FOSQ-10 total scores at the end of the long-term study for the total population and for the OSA subgroup approached normative values.[20]

The safety profile observed in the present study was similar in participants with narcolepsy and those with OSA, with roughly 9.2% of participants discontinuing the study due to AEs, a rate consistent with those seen in other long-term treatment studies in populations with EDS associated with narcolepsy, OSA, or shift work disorder (9–13%).[30–32] Although no new common TEAEs were reported in either patient subset of this long-term study, overall incidence of any TEAE (74.8%) and any serious TEAE (2.7%) in the narcolepsy group was slightly higher than that reported in the 12-week phase 3 study of solriamfetol for patients with narcolepsy (68.4% and 0.6%, respectively).[13] Similarly, the incidence of any TEAE (75.1%) and any serious TEAE (5.0%) in the present study was higher than that observed in the 12-week phase 3 study of solriamfetol for patients with OSA (67.9% and 0.8%, respectively).[14] In addition to AEs, the other most common reason for discontinuation was lack of efficacy. A higher percentage of participants with narcolepsy discontinued due to lack of efficacy than participants with OSA (17.3% vs 3.6%),[16] which may reflect the greater severity of disease and/or be due to the fact that other medications used to treat EDS were prohibited.

There is a paucity of available information regarding long-term risks and benefits of established therapies for EDS associated with narcolepsy and residual EDS in treated OSA. Although short-term studies are important, long-term data are essential to inform clinical decision making for long-term care of patients with chronic disease. Therefore, a strength of the current study is the 1-year duration. Furthermore, short-term studies with

stimulants have shown improvements in EDS; however, it is not clear whether long-term reductions in sleepiness translate to other clinically meaningful improvements in functioning, HRQoL, or work productivity. For example, caffeine has been shown to improve alertness in the setting of sleep deprivation,[33] but data are lacking to support the use of caffeine as a long-term strategy for improving QoL or work place performance. The current analyses demonstrate that solriamfetol improves daily functioning, HRQoL, and work productivity, in addition to EDS, with long-term treatment and in a similar manner as what has been previously reported with shorter-term treatment.[6,16,17]

Importantly, pharmacologic treatment for EDS should not replace primary treatment for the underlying cause of EDS. Solriamfetol is not indicated to treat the underlying airway obstruction in OSA; therefore, it is critical to encourage OSA patients to use a therapy that treats the underlying airway obstruction.[11] CPAP is the gold standard treatment for OSA, but adherence to therapy is variable.[34] Data support the optimization of CPAP adherence such that greater improvements in outcomes are observed with increased CPAP usage.[35] Notably, a separate analysis of participants in the current study indicated that solriamfetol did not have a clinically meaningful effect on primary OSA therapy adherence.[36] However, even with optimal adherence, some OSA patients will continue to experience residual EDS.[1,2] The mechanism underlying this observation has been debated and may involve injury to the periaqueductal gray region.[37] Human studies have also shown white matter compromise in OSA patients with residual EDS, including myelin diffusivity and axonal shrinkage.[38,39] Regardless of the mechanism underlying persistent EDS in OSA, population estimates indicate that 9–22% of CPAP-treated patients may have residual EDS.[1,2] In addition, many OSA patients have nonspecific complaints, including fatigue, nonrestorative sleep, and the need for caffeine, and many patients with narcolepsy have persistent symptoms that could benefit from the use of 1 or more medications.

Despite the strengths of the current study, there were a number of limitations. First, no direct comparisons with other stimulant or wake-promoting therapies were conducted; therefore, it is inconclusive whether one therapy is more effective and/or has a more tolerable side effect profile than another. A number of wake-promoting agents have been evaluated in open-label long-term studies and have demonstrated long-term efficacy under open-label conditions. For example, modafinil and armodafinil have been investigated in open-label, long-term extension studies in participants with narcolepsy or OSA, with data suggesting long-term efficacy in reducing EDS.[30,40] Long-term studies of these agents in populations with narcolepsy or OSA have also demonstrated improvements in QoL measures, including the SF-36v2, FOSQ-10, and Brief Fatigue Inventory.[30,41,42] Pitolisant has also demonstrated long-term efficacy in reducing EDS in participants with narcolepsy, as well as improvement in patient-reported health status as assessed by the European Quality of Life Questionnaire visual analog scale.[43] Future research evaluating the comparative effectiveness of these various pharmacotherapies may be beneficial.

In addition, based on the long-term extension study design, participants were recruited from different studies and, as a result, participants who did not complete the parent studies were, by design, not eligible for long-term extension assessments. In theory, participants who discontinued the parent studies are likely to be less amenable to therapy, based on either lack of efficacy or occurrence of side effects. Although the design of the parent studies (ie, randomization to a specific treatment arm and inclusion of a placebo group) may affect the extent to which such an assumption holds in the current study, it should be noted that including only participants who completed a prior clinical trial may overestimate treatment effects and minimize intolerability and side effects in a long-term extension study. Despite this, the current study population is generalizable to the real-world patient population seeking treatment for EDS with a wake-promoting agent based on baseline demographics, disease characteristics, and underlying comorbidities. Future subgroup analyses to identify patients who are likely to be maximally responsive with minimal side effects would be informative. Despite these limitations, these findings provide important insights into the sustained treatment of patients with narcolepsy or OSA.

CONCLUSIONS

Long-term treatment with solriamfetol was associated with clinically meaningful, sustained improvements in functional status, work productivity, and HRQoL in participants with narcolepsy and OSA for up to 52 weeks. TEAEs associated with long-term solriamfetol treatment included headache, nausea, nasopharyngitis, insomnia, dry mouth, anxiety, decreased appetite, and upper respiratory tract infection and were similar between participants with narcolepsy and those with OSA.

ABBREVIATIONS

AE, adverse event
CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
FOSQ-10, Functional Outcomes of Sleep Questionnaire short version
HRQoL, health-related quality of life
OSA, obstructive sleep apnea
QoL, quality of life
SD, standard deviation
SF-36v2, Short Form Health Survey version 2
TEAE, treatment-emergent adverse event
WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

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Address correspondence to: Terri E. Weaver, PhD, RN, FAAN, ATSF, Dean, Professor, Department of Biobehavioral Health Science College of Nursing, Professor, Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, College of Medicine, University of Illinois Chicago, 845 S. Damen Ave., MC 802, Chicago, IL 60612; Tel: (312) 996-7808; Fax: (312) 413-4399; Email: teweaver@uic.edu

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