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SCIENTIFIC INVESTIGATIONS

Effects of solriamfetol in a long-term trial of participants with obstructive sleep apnea who are adherent or nonadherent to airway therapy

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Study Objectives: Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, is approved in the United States and European Union to treat excessive daytime sleepiness in patients with obstructive sleep apnea (OSA) (37.5–150 mg/day) and narcolepsy (75–150 mg/day). This analysis evaluated solriamfetol's efficacy in subgroups of participants with OSA who were adherent or nonadherent to primary OSA therapy at baseline and examined whether solriamfetol affected the use of primary therapy in an open-label extension trial.

Methods: Participants with OSA who completed prior solriamfetol studies received solriamfetol 75, 150, or 300 mg/day for ≤ 52 weeks. The main efficacy outcome was the Epworth Sleepiness Scale score. Primary therapy use was summarized as the percentage of nights, the number of hours/night, and the percentage of nights with use ≥ 50%/night (%). Efficacy and primary therapy use are reported for participants who directly enrolled from a previous 12-week study and had ≤ 40 weeks of open-label treatment (n = 333). Safety data are reported for all participants (n = 417).

Results: Mean ESS scores in adherent (n = 255) and nonadherent (n = 78) subgroups, respectively, were 15.0 and 15.8 at baseline (of 12-week study) and 6.5 and 6.8 at week 40. For participants using an airway therapy, mean use at baseline was 90% of nights, 6.6 hours/night, and use ≥ 50%/night on 90% of nights; changes from baseline to week 40 were minimal (0.9%, −0.8 hours, and 6.5%, respectively). Common adverse events (both subgroups) included headache, nasopharyngitis, insomnia, dry mouth, nausea, anxiety, and upper respiratory tract infection.

Conclusions: Long-term efficacy and safety of solriamfetol were similar regardless of adherence to primary OSA therapy. Solriamfetol did not affect primary therapy use.

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; URL: https://clinicaltrials.gov/ct2/show/NCT02348632; Identifier: NCT02348632 and Registry: EU Clinical Trials Register; Identifier: 2014-005489-31; URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-005489-31.

Keywords: JZP-110; Sunosi; excessive daytime sleepiness; treatment adherence and compliance; lung; CPAP; oral appliance

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The current study evaluated the efficacy and safety of long-term treatment of excessive daytime sleepiness with solriamfetol in subgroups of participants with obstructive sleep apnea (OSA) who were adherent or nonadherent to primary therapy for OSA therapy. In addition, this study evaluated whether long-term solriamfetol treatment impacted participants' use of primary OSA therapy.

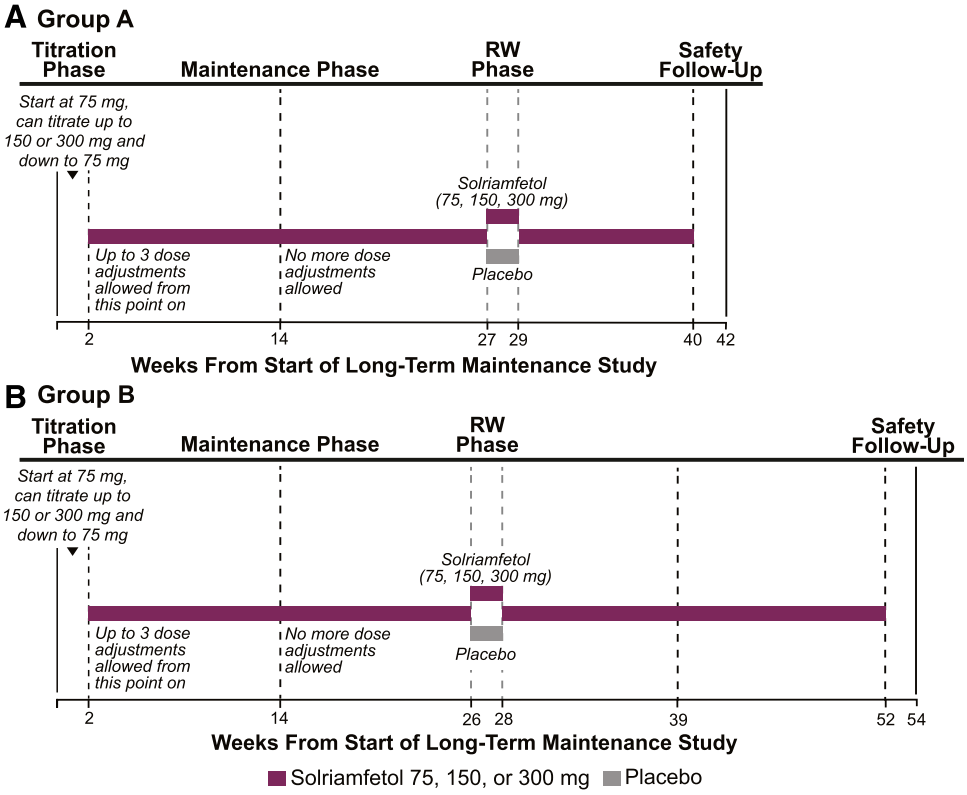
Study Impact: The magnitude of solriamfetol's wake-promoting benefit is similar regardless of adherence to primary OSA therapy. Further, the level of primary OSA therapy use remained acceptable based on current standards with no meaningful changes over 40 weeks of solriamfetol treatment, demonstrating that long-term treatment of excessive daytime sleepiness with solriamfetol does not impact patients' use of primary OSA therapy.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a cardinal feature of obstructive sleep apnea (OSA),[1–3] which is estimated to affect nearly one billion individuals worldwide.[4] Literature suggests that both objective and self-reported sleepiness are common in most patients with OSA who consult a clinic.[5] Therapy with continuous positive airway pressure (CPAP) and oral appliances has improved EDS in some patients, particularly those who are adherent to therapy[2,6–8]; however, even in patients who use their OSA therapy in an adherent manner (> 6 hours/night), residual EDS may occur. For example, it is reported that an estimated 9% to 22% of CPAP-treated patients have residual EDS in population-based studies.[9,10] The underlying mechanisms of residual EDS in OSA are unclear.[11–17]

Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, has been approved in the United States and in the European Union to improve wakefulness in adult patients with EDS associated with OSA or narcolepsy.[18,19] The approved dose range of solriamfetol is 37.5 to 150 mg once daily for patients with OSA and 75 to 150 mg once daily for patients with narcolepsy.[18,19] Previously published data from

Figure 1—Study design.



Group A enrolled immediately after the 12-week study. Group B subsequently enrolled after one of several previous solriamfetol studies. Not all participants took part in the RW phase. RW, randomized withdrawal. Adapted from Malhotra A, Shapiro C, Pepin JL, et al. Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep*. 2020;43(2):zsz220.

short-term (12 weeks) and long-term (up to 1 year) phase 3 studies demonstrated robust wake-promoting effects of solriamfetol in participants with OSA.[20,21] In the 12-week study, subgroup analyses showed that solriamfetol produced similar improvements in EDS in participants who were adherent and those who were nonadherent to primary OSA therapy at baseline and did not affect primary OSA therapy use.[22] The current analyses aimed to evaluate the efficacy and safety of long-term solriamfetol treatment in subgroups of participants who were adherent or nonadherent to primary OSA therapy. In addition, the impact of long-term treatment with solriamfetol on adherence to primary OSA therapy was examined.

METHODS

Study design

This 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 (https://www.clinicaltrials.gov identifier NCT02348632, and https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005489-31/results). Full details on the methods of the study have been previously reported[21] and are briefly summarized here.

This was a long-term study that evaluated the efficacy and safety of solriamfetol in adults with OSA or narcolepsy who had previously completed randomized placebo-controlled trials of solriamfetol (including NCT02806895/Eudra CT 2015-003930-28 and NCT02806908/Eudra CT 2015-003931-36 and several trials with published results[20,23–26]). The study included two groups: group A (n = 333) included participants who enrolled immediately after completion of the parent study, and group B (n = 84) included participants who enrolled at a later time. After titration of open-label solriamfetol over a 2-week period, participants entered an open-label maintenance phase for a total open-label study duration of 40 weeks (group A) or 52 weeks (group B) (**Figure 1**). At approximately 6 months into the maintenance phase, a subgroup of participants was randomized to placebo or continued treatment with solriamfetol for 2 weeks, after which open-label maintenance treatment resumed. For the current analyses of primary OSA therapy adherence and efficacy, this article focuses on the subset of participants with OSA from group A (n = 333), as this represents the largest cohort of participants with OSA who had long-term exposure to solriamfetol; safety data were analyzed for group A and group B combined and are reported as such.

Participants

Eligibility criteria for the parent studies for participants with OSA included age 18 to 75 years, diagnosis of OSA based on

International Classification of Sleep Disorders third edition criteria, and either use of a primary therapy for OSA (ie, CPAP, oral pressure therapy, oral appliance, or upper airway stimulator), history of an OSA primary therapy use attempt, or history of surgical intervention to treat OSA symptoms.

In addition to completion of a previous clinical trial of solriamfetol, eligibility criteria for the extension study included a body mass index from 18 to < 45 mg/m^2 and usual nightly sleep of at least 6 hours. Participants were excluded if they experienced any serious adverse event in a previous study that was considered related to solriamfetol. Other key exclusion criteria included a usual bedtime later than 1:00 AM, an occupation requiring nighttime or variable shift work, any disorder other than OSA (or narcolepsy) that is associated with EDS, excessive caffeine use (> 600 mg/d) during the study, and use of any over-the-counter or prescription medications that could affect the evaluation of EDS.

Treatment

Participants initiated open-label solriamfetol starting at 75 mg/day during a 2-week titration phase; the 75-mg initial dose could be increased during the titration phase to 150 mg and then 300 mg in intervals of no fewer than 3 days or decreased at any time for safety reasons (**Figure 1**). The dose at the end of the titration phase was carried into the maintenance phase and could be adjusted up to three times within the first 12 weeks of maintenance treatment.

After approximately 6 months of treatment, a subgroup of participants entered a 2-week randomized withdrawal phase, with participants either continuing solriamfetol treatment or switching to placebo for 2 weeks. After the withdrawal phase, those randomized to placebo returned to their solriamfetol dose either immediately (those receiving 75 mg/day) or after 3 days at either 75 mg/day for (those receiving 150 mg/day) or 150 mg/day (for those receiving 300 mg/day).

Participants using an OSA primary therapy device at baseline were instructed to maintain the same level of use throughout the study.

Outcomes

Efficacy end points for solriamfetol treatment included the Epworth Sleepiness Scale (ESS) score[27] and percentages of participants showing improvement according to the Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C) scales.[28] Efficacy assessments were conducted at weeks 2, 14, 27, and 40. The effect of treatment on participant functioning was assessed via Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10) total score,[29] which was administered at weeks 14, 27, and 40. All assessments were also administered at early termination visits occurring after week 2. Data from the 2-week randomized withdrawal phase were excluded for the subset of patients who participated in this phase (weeks 28 and 29).

For the purpose of defining subgroups of participants who were adherent or nonadherent to OSA primary therapy at baseline, *adherence* was defined as device use for at least 4 hours per night on at least 70% of nights for devices with downloadable data; device use on at least 70% of nights for devices with no downloadable data; or effective surgical intervention.

For participants using devices as primary OSA therapy (at any level of adherence), use during the study was obtained by digitally recorded output from a positive airway pressure (PAP), oral appliance, or hypoglossal nerve stimulator device, when available, or by diary. Data on the use of OSA therapy were summarized by the percentage of nights used (from electronically retrievable and diary data), the number of hours/night for those with electronically retrievable information, and the percentage of nights used more than half of the night for those who completed a diary.

Safety and tolerability assessments included treatment-emergent adverse events (TEAEs).

Statistical analysis

Open-label efficacy data and TEAEs were analyzed in the *safety population*, defined as all participants who received at least one dose of study medication, and data were summarized descriptively for subgroups based on baseline adherence or nonadherence to OSA primary therapy. We input missing data by using a last-observation-carried-forward approach for the ESS, PGI-C, and CGI-C, but not for the FOSQ-10. Primary OSA therapy device use was summarized descriptively.

Because of the differing time points of treatment initiation for groups A and B, efficacy and primary OSA therapy use data were summarized and analyzed separately for these groups, with baseline defined for group A as the baseline of the parent study and for group B as the baseline of the open-label study. For simplicity and given that group A comprised most (80%) of the study population for these analyses, efficacy and primary OSA therapy use data are presented only for group A. Findings for group B were similar (data not shown). Safety data are reported for the entire safety population (groups A and B combined).

RESULTS

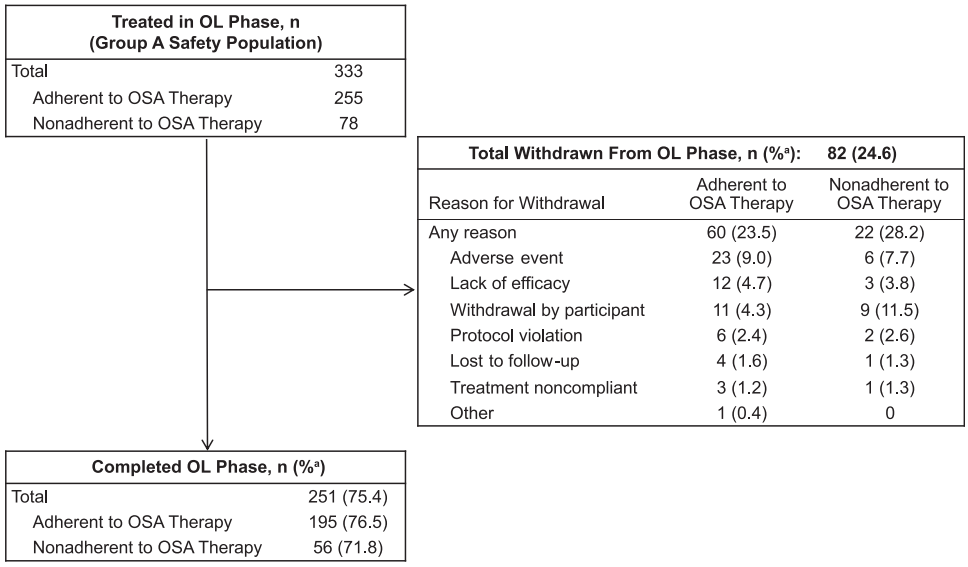
Population

The safety population included 417 participants with OSA (group A, n = 333; group B, n = 84). Of the 333 participants in group A, 251 (75.4%) completed the study; adverse events were the most common reason for discontinuation (8.7%) (**Figure 2**).

At baseline, 235 (70.6%) participants in group A reported using a primary OSA therapy (based on diary information). Of these, most (n = 222) were using PAP as the primary therapy; of those not using PAP, 3 were using device therapy, and 12 were using another primary therapy not specified (sum of n values exceeds total because some participants reported more than one type of primary OSA therapy). A history of surgical intervention was reported for 48 participants. Among the 48 participants with surgical intervention, all were using primary OSA therapy at baseline; 47 participants (43 in the adherent subgroup; 4 in the nonadherent subgroup) were using PAP, and 1 (in the adherent subgroup) was using oral appliance therapy.

Group A included 255 participants who met the definition for adherence with primary OSA therapy at baseline and 78 who did not (ie, were nonadherent). Mean age and body mass index were similar for both subgroups, whereas the adherent subgroup

Figure 2—Participant disposition (group A).



[a]Percentage based on number of participants treated as denominator (total, n = 333; adherent, n = 255; nonadherent, n = 78). OL = open label, OSA = obstructive sleep apnea.

Table 1—Baseline demographics and disease characteristics (group A).

Characteristic[a]	Group A	
	Adherent (n = 255)	Nonadherent (n = 78)
Age (y), mean (SD)	55 (11.0)	52 (11)
Male, n (%)	160 (62.7)	43 (55.1)
Race, n (%)		
Black or African-American	35 (13.7)	24 (30.8)
White	212 (83.1)	48 (61.5)
Other or multiple	8 (3.1)	6 (7.7)
Body mass index (kg/m^2), mean (SD)	33.8 (5.4)	32.8 (4.8)
ESS total score, mean (SD)	15.0 (3.2)	15.8 (3.6)
FOSQ-10 total score, mean (SD)	14.0 (3.0)	13.9 (3.1)

ESS = Epworth Sleepiness Scale, FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, SD = standard deviation. [a]Baseline data represent baseline of the parent study.

had higher percentages of participants who were male and participants who were white (**Table 1**). Mean baseline ESS and FOSQ-10 scores were similar in participants who were adherent and nonadherent to primary OSA therapy at baseline.

Efficacy by OSA primary therapy adherence

The mean change in ESS scores over time for group A reflects improvements that began in the parent study (ie, from baseline of parent study) and continued throughout the maintenance phase to week 40 of the open-label study (**Figure 3**). Specifically, the magnitude of change in ESS scores with solriamfetol resulted in mean ESS scores in the normative range (≤ 10)[27] for the duration of open-label treatment. These decreases were similar regardless of adherence to OSA primary therapy and were sustained throughout the open-label study for both subgroups.

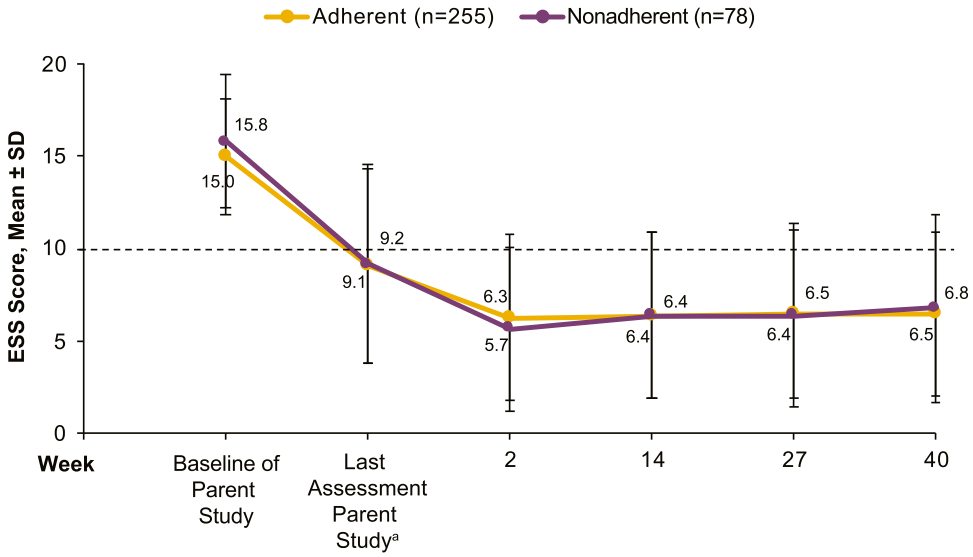
At week 2 of the open-label study, rates of overall improvement from baseline on the PGI-C (**Figure 4A**) and CGI-C (**Figure 4B**) in group A were greater than 90% in both the adherent and nonadherent subgroups and were generally sustained throughout the maintenance phase to week 40.

Mean FOSQ-10 scores improved over time to a level consistent with that of individuals without sleep disorders (cut point of 17.9),[29,30] with similar effects observed independent of primary OSA therapy adherence status (**Figure 5**).

Effect of solriamfetol treatment on OSA primary therapy adherence

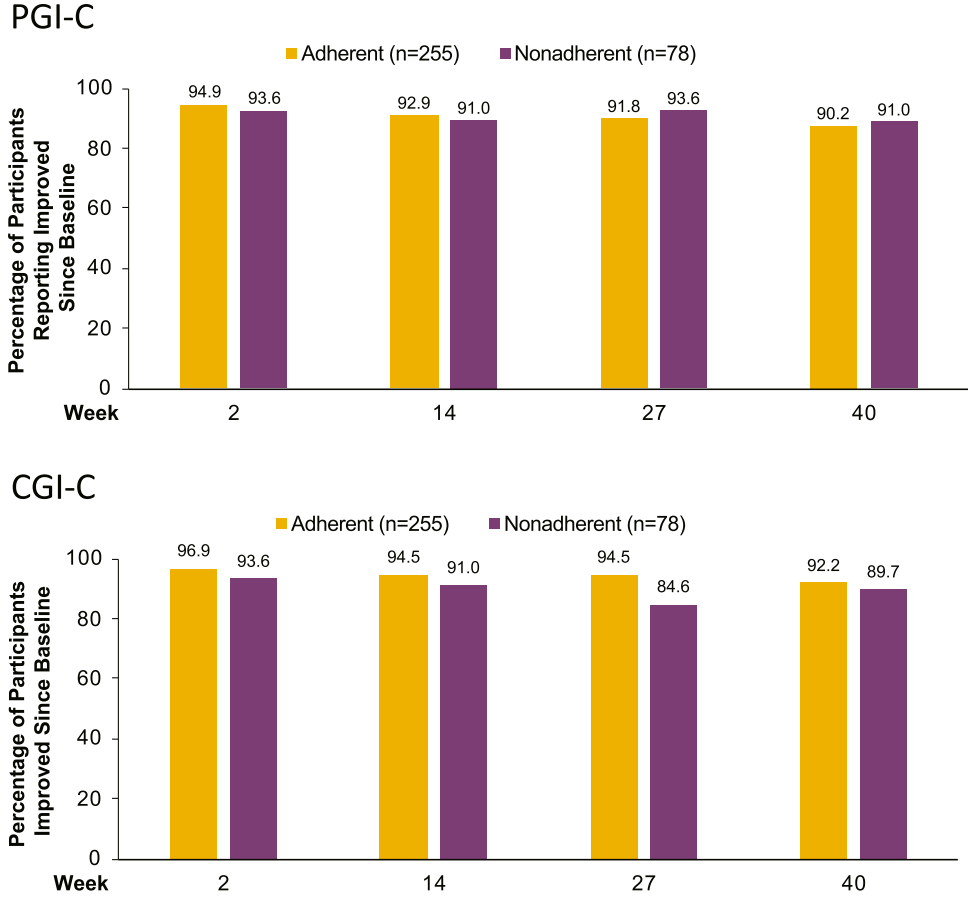
Among group A participants who used a primary OSA therapy, the mean and median observed values for use data were generally consistent over the course of the study (**Table 2**). This consistency was also reflected in the minimal change from baseline over the open-label study, which ranged from mean changes of −0.5 to 2.0 for percentage of nights, −1.0 to −0.7 for number of hours/night, and 3.6 to 6.5 for the percentage of

Figure 3—Epworth Sleepiness Scale (ESS) score by OSA primary therapy adherence (group A).



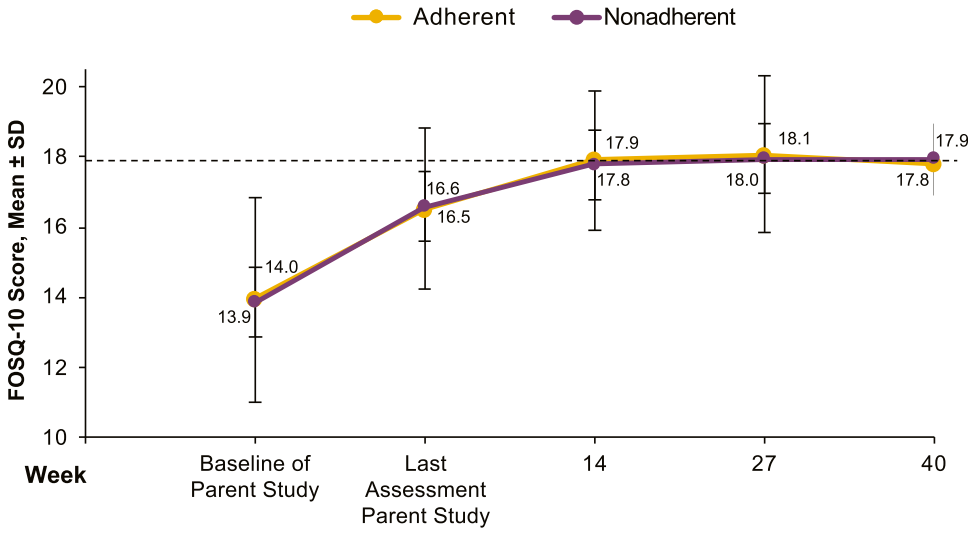
Missing data imputed using last observation carried forward. Dashed line represents normative ESS score (10).[27] [a]Not all participants at the last assessment in the parent study were on study drug. OSA = obstructive sleep apnea, SD = standard deviation.

Figure 4—Participant- and clinician-reported improvement from baseline by OSA primary therapy adherence (group A).



Missing data imputed using last observation carried forward. CGI-C = Clinical Global Impression of Change, OSA = obstructive sleep apnea, PGI-C = Patient Global Impression of Change.

Figure 5—Functional Outcomes of Sleep Questionnaire-10 score by OSA primary therapy adherence (group A).



Observed data: adherent subgroup (n = 255 at parent study baseline and last assessment of parent study; n = 195 at week 40) and nonadherent subgroup (n = 78 at parent study baseline and last assessment of parent study; n = 56 at week 40). Dashed line represents normative FOSQ-10 score (17.9).[29,30]
FOSQ-10 = Functional Outcomes of Sleep Questionnaire short version, OSA = obstructive sleep apnea, SD = standard deviation.

nights used more than half the night. Data were summarized separately for group A participants who did not participate in the randomized withdrawal phase (ie, weeks 28–40) and for those who did participate in the randomized withdrawal phase (weeks 30–40); use data during the final study period remained stable in both subgroups.

There did not appear to be a substantial number of participants who remained in the study but did not report primary OSA therapy use. Among all 202 participants with either electronically retrievable or diary data (summarized as percentage of nights) who remained in the study before the final period (represented as weeks 28–40), only 16 (7.9%) participants were not accounted for in the final period because they either did not report primary OSA therapy use, or they discontinued from the study.

Safety

During the open-label study, 74.3% (310/417) of participants reported at least one TEAE, with similar rates of overall TEAEs, serious TEAEs, and TEAEs leading to discontinuation among those who were or were nonadherent to OSA primary therapy at baseline (**Table 3**). One death attributed to sepsis was deemed unrelated to study medication. The most common TEAEs overall were headache (40/417, 9.6%), insomnia (35/417, 8.4%), nasopharyngitis (33/417, 7.9%), and dry mouth (33/417, 7.9%), which occurred at comparable rates in participants who were adherent or nonadherent to OSA primary therapy at baseline.

DISCUSSION

Prior data have shown the robust effects of long-term solriamfetol treatment in improving EDS in the overall OSA population.[21] Results from the current analysis expand on these findings, demonstrating efficacy is similar, regardless of adherence or nonadherence to primary OSA therapy.[20,21] Specifically, the magnitude of the benefit from the standpoint of the ESS, FOSQ-10, and PGI-C/CGI-C was similar in participants with and without adherence to OSA therapy. In addition, long-term use of solriamfetol did not negatively affect adherence to primary OSA therapy for up to 1 year. Among participants for whom electronically retrievable data were available, OSA therapy was used between a median of 6.1 and 6.6 hours per night across the open-label extension, an acceptable duration given the current literature and standards.[30]

The finding that solriamfetol treatment did not impact primary OSA therapy use is generally consistent with findings from studies of other wake-promoting agents approved for the treatment of EDS associated with OSA (eg, modafinil and armodafinil),[31,32] suggesting that pharmacotherapy does not clinically impact CPAP adherence. Several placebo-controlled studies have shown that adherence to CPAP is similar with modafinil/armodafinil and placebo,[33–35] whereas others have reported small but statistically significant reductions in nightly duration of CPAP use with modafinil/armodafinil (−0.2 to −0.4 hours/night).[36,37]

The underlying mechanisms of residual EDS in OSA are likely multifactorial. Some studies have suggested that CPAP therapy itself may disrupt sleep physiology and that elimination of apnea may not normalize sleep effectiveness in this context.[38,39] Others have suggested that permanent neuronal injury, in sites like the locus coeruleus and periaqueductal gray, and alterations in brain white matter may account for residual EDS in patients who are adherent to OSA treatment.[11–17] In some patients, periodic limb movements, sedating medications, suboptimal CPAP adherence, chronic partial sleep deprivation,

Table 2—OSA primary therapy device use over time (group A).

	Observed Value			Change from Baseline		
	N[a]	Mean (SD)	Median (Q1, Q3)	n[a]	Mean (SD)	Median (Q1, Q3)
Percentage of nights[b]						
Baseline	235	90.0 (19.1)	100.0 (89.3, 100.0)	—	—	—
Day 1 to week 2	248	89.0 (23.9)	100.0 (92.9, 100.0)	228	1.4 (13.3)	0.0 (0.0, 5.44)
Week 3 to 14	234	87.1 (26.1)	98.9 (88.8, 100.0)	214	−0.5 (15.2)	0.0 (−1.2, 4.6)
Week 15 to 27	212	88.2 (25.0)	100.0 (90.8, 100.0)	197	0.3 (13.0)	0.0 (−1.1, 4.55)
Week 28 to 40[c]	186					
Week 28 to 40	68	89.2 (22.9)	100.0 (90.7, 100.0)	62	2.0 (12.3)	0.0 (0.0, 4.55)
Week 30 to 40	118	89.5 (24.0)	100.0 (94.7, 100.0)	109	0.9 (12.4)	0.0 (0.0, 5.14)
No. of hours per night[d]						
Baseline	147	6.6 (1.4)	6.6 (5.8, 7.4)	—	—	—
Day 1 to week 2	138	5.9 (2.1)	6.4 (4.8, 7.4)	126	−0.7 (1.5)	−0.4 (−1.2, 0.2)
Week 3 to 14	134	5.7 (2.1)	6.1 (4.9, 7.1)	120	−1.0 (1.7)	−0.6 (−1.5, 0.0)
Week 15 to 27	116	5.9 (2.1)	6.2 (5.1, 7.2)	106	−0.9 (1.6)	−0.5 (−1.5, 0.0)
Week 28 to 40[c]	102					
Week 28 to 40	40	5.9 (2.1)	6.1 (5.2, 7.4)	34	−0.9 (1.4)	−0.8 (−1.5, 0.0)
Week 30 to 40	62	6.0 (2.0)	6.4 (5.4, 7.0)	58	−0.8 (1.7)	−0.5 (−1.1, 0.2)
Percentage of nights OSA device was used more than half of night[e]						
Baseline	89	90.4 (26.1)	100.0 (100.0, 100.0)	—	—	—
Day 1 to week 2	111	91.5 (23.2)	100.0 (100.0, 100.0)	83	4.1 (16.8)	0.0 (0.0, 0.0)
Week 3 to 14	100	94.5 (18.8)	100.0 (100.0, 100.0)	76	5.3 (19.3)	0.0 (0.0, 0.0)
Week 15 to 27	95	92.7 (21.8)	100.0 (100.0, 100.0)	73	3.6 (19.9)	0.0 (0.0, 0.0)
Week 28 to 40[c]	83					
Week 28 to 40	27	94.4 (19.7)	100.0 (100.0, 100.0)	22	6.2 (21.8)	0.0 (0.0, 0.0)
Week 30 to 40	56	94.7 (18.9)	100.0 (100.0, 100.0)	42	6.5 (20.5)	0.0 (0.0, 0.0)

OSA = obstructive sleep apnea, Q1 = 25th percentile, Q3 =75th percentile, SD = standard deviation. [a]No. of participants with nonmissing value at visit. [b]Among all participants (with either electronically retrievable or diary data). [c]Data for this period were summarized separately for participants who did not enter the randomized withdrawal phase (week 28 to 40) and for participants who entered the 2-week randomized withdrawal phase (week 30–40). [d]Among participants with electronically retrievable data. [e]Among participants with diary data.

idiopathic hypersomnia, and other conditions may contribute to residual EDS; these conditions were excluded in the current study. Addressing underlying causes should be considered the first-line approach to treatment of residual EDS in OSA; however, in clinical practice, a high percentage (~30%) of patients with OSA have residual EDS, despite adherence to primary OSA therapy. In addition, population-based studies have estimated that 9%–22% of CPAP-treated patients continue to have residual EDS.[9,10] Therefore, many patients with EDS associated with OSA may benefit from wake-promoting agents

Table 3—Treatment-emergent adverse events by OSA primary therapy adherence (safety population).[a]

TEAE, n (%)	Adherent (n = 324)	Nonadherent (n = 93)
At least 1 TEAE	249 (76.9)	61 (65.6)
Serious TEAE	17 (5.2)	3 (3.2)
TEAEs leading to discontinuation	29 (9.0)	7 (7.5)
Death	1 (0.3)[b]	0 (0.0)
Common TEAEs[c]		
Headache	30 (9.3)	9 (9.7)
Insomnia	28 (8.6)	7 (7.5)
Nasopharyngitis	25 (7.7)	8 (8.6)
Anxiety	24 (7.4)	1 (1.1)
Dry mouth	23 (7.1)	10 (10.8)
Nausea	23 (7.1)	8 (8.6)
Feeling jittery	20 (6.2)	5 (5.4)
Upper respiratory tract infection	19 (5.9)	2 (2.2)
Dizziness	17 (5.2)	2 (2.2)
Decreased appetite	8 (2.5)	6 (6.5)

OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event. [a]Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. [b]From sepsis (deemed not related to study drug). [c]≥5% in combined solriamfetol groups.

and subsequent improvements in quality of life or reductions in the risk of sleepiness-related complications.[20]

For nonadherent patients, efforts to improve adherence or seek alternative therapies are necessary to address the primary airway obstruction. Many patients who have been prescribed CPAP and who struggle with achieving and maintaining high levels of adherence to therapy can benefit from intensive support, troubleshooting of mask/interface, addressing nasal congestion, improving sleep hygiene, desensitization, and other strategies.[40–44] Oral appliances have acceptable results compared with PAP therapy and thus should also be considered in patients for whom PAP therapy fails or who cannot use this therapy.[8,45] Hypoglossal nerve stimulation, major weight loss, and other strategies might be appropriate for some patients.[46,47] Despite these efforts, some patients with OSA might still be undertreated or may take considerable time to achieve alternative therapies (eg, major weight loss, adjustment to a customized oral appliance, or surgical alternatives). Thus, these patients may also benefit from treatment with solriamfetol so long as such treatment is not considered a substitute for therapy that would relieve hypoxemia and recurrent arousal.

A major strength of the current study was inclusion of participants with varying levels of adherence to primary OSA therapy, thus providing a study population representative of patients in real-world clinical practice. Despite its strengths, the study had several important limitations. First, there was no placebo group in the open-label maintenance phase, and therefore results could not be compared with placebo. In addition, the observed effects of solriamfetol were not compared with those of other wake-promoting agents. Second, the impact of the missing primary OSA therapy use data needs to be considered. Some patients dropped out of the study, and others remained but did not report therapy use, leaving open the question of whether they discontinued use of their primary OSA therapy device; however, the number of participants who remained in the study but did not report primary OSA therapy use data was not substantial. Further, findings from the 12-week placebo-controlled study indicate that some placebo-treated participants remained in the study but did not report primary OSA therapy use data (Paula K. Schweitzer, PhD; Geert Mayer, MD; Russell Rosenberg, PhD; Atul Malhotra, MD; Gary K. Zammit, PhD; Mark Gotfried, MD; Patricia Chandler, MD; Michelle Baladi, PhD; Kingman P. Strohl, MD; manuscript submitted for publication, November 2020). Thus, it appears that there is no impact of short- or long-term treatment with solriamfetol on primary OSA therapy use; however, participants were instructed to keep their primary OSA therapy use consistent throughout the study. Encouragement of consistent use of CPAP therapy may not occur as regularly in clinical practice; therefore, reinforcement of this instruction in a clinical trial setting is also a limitation. Finally, given the nature of the clinical trial design, there may have been a selection bias whereby the most motivated participants were the ones likely to participate and to follow through with long-term extension visits. Thus, the study may have been subject to the "healthy user effect" whereby the most motivated participants may have had the best outcomes.[48] As a result, it is unclear how much the current clinical trial findings will generalize to clinical practice, as the two settings may differ in the motivation levels of their participants and in the instructions participants are given.

Notably, in the current study, the safety profile was similar between participants who were adherent and those who were nonadherent to primary OSA therapy, suggesting there are no additional safety concerns associated with solriamfetol treatment for patients who are nonadherent to CPAP.

In conclusion, these findings show that the magnitude of the wake-promoting effects of solriamfetol treatment for up to 1 year is similar regardless of adherence to primary OSA therapy. In addition, the level of primary OSA therapy use remained unchanged over the duration of solriamfetol treatment, demonstrating that long-term treatment of EDS with solriamfetol does not affect patients' use of primary OSA therapy.

ABBREVIATIONS

CGI-C, Clinical Global Impression of Change
CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
FOSQ-10, Functional Outcomes of Sleep Questionnaire-10
OSA, obstructive sleep apnea
PAP, positive airway pressure
PGI-C, Patient Global Impression of Change
TEAE, treatment-emergent adverse event

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