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Sleep Medicine 100 (2022) 165–173

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Effects of solriamfetol treatment on body weight in participants with obstructive sleep apnea or narcolepsy

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ARTICLE INFO

Article history:
Received 3 December 2021
Received in revised form
5 August 2022
Accepted 8 August 2022
Available online 14 August 2022

Keywords:
Solriamfetol
Sunosi
JZP-110
Lung
Sleep apnea
Obesity

ABSTRACT

Objectives: This analysis characterized changes in weight in participants with obstructive sleep apnea (OSA) or narcolepsy treated with solriamfetol (Sunosi™) 37.5 (OSA only), 75, 150, or 300 mg/d.
Methods: In two 12-week, randomized, placebo-controlled trials and one 1-year open-label extension study, changes in weight were evaluated from baseline to end of study (week 12 or week 40 of the open-label extension [after up to 52 weeks of solriamfetol treatment]) in participants with OSA or narcolepsy.
Results: After 12 weeks of solriamfetol treatment, median percent change in weight from baseline across all solriamfetol doses was −0.84%, compared with 0.54% for placebo, in participants with OSA; and −0.07%, compared with 3.08% for placebo, in participants with narcolepsy. After up to 52 weeks of solriamfetol treatment, overall median percent change in weight from baseline was −1.76%, which showed a dose-dependent pattern (75 mg, 0.57%; 150 mg, −1.2%; 300 mg, −2.5%). Results were similar in subgroups of participants with OSA or narcolepsy, with overall median percent changes in weight of −2.2% and −1.1%, respectively. After up to 52 weeks of solriamfetol treatment, the percentage of participants with weight loss ≥5% relative to baseline was 25.7% overall and increased in a dose-dependent manner (75 mg, 4.5%; 150 mg, 17.3%; 300 mg, 32.4%). Results were similar among subgroups of participants with OSA or narcolepsy, with 26.4% and 24.2% of participants experiencing weight loss ≥5%, respectively. No weight-related treatment-emergent adverse events were serious.
Conclusions: Solriamfetol treatment was associated with decreases in body weight in a dose-related manner.

1. Introduction

Diet, exercise, and sleep have been described as the 3 pillars of health, with the dogma often stated that if one is ignored, the other two might suffer. Insufficient sleep (ie, sleeping less than the recommended amount of 7–9 h per night) [1,2] has been associated with increased body weight, higher body mass index (BMI), as well as increased risk of obesity, as compared with people sleeping 7–9 h per night [2–5]. Sleep disorders, including obstructive sleep

Abbreviations: BL, baseline; EDS, excessive daytime sleepiness; OLE, open-label extension; OSA, obstructive sleep apnea.

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https://doi.org/10.1016/j.sleep.2022.08.005

apnea (OSA) and narcolepsy, have been associated with overweight and obesity, with potential risk of cardiometabolic sequelae [6–10]. While the precise mechanistic link between narcolepsy and weight gain is unclear, loss of orexin signaling is associated with impaired development and function of brown adipose tissue [11], as well as metabolic abnormalities in animal models (eg, late-onset obesity preceded by hypophagia, suggesting reduced energy expenditure) [12], highlighting the role of orexin not only in regulating sleep but also energy metabolism. Treatment of OSA with continuous positive airway pressure (CPAP) has consistently been associated with moderate weight gain, leading to concern regarding potential mixed effects of CPAP on overall health [13,14]. Thus, efforts to facilitate weight loss in patients with sleep disorders would be potentially beneficial.

The role of sleep specialists in managing body weight has been debated, but many feel that addressing diet and exercise is standard of care [15]. In a randomized trial evaluating treatment options for OSA, Chirinos et al. [16] compared the effects of a weight loss intervention, CPAP therapy, or a combination of a weight loss intervention plus CPAP. The data strongly supported the role of weight loss in mitigating cardiometabolic risk in patients with OSA, although the combination of the 2 treatments (CPAP plus weight loss) was likely more effective than either treatment alone. These findings suggest that efforts to promote weight loss in patients with OSA would have therapeutic benefit for overall health. Behavioral, pharmacologic, or mechanical approaches to treating obesity have all been discussed, but evidence evaluating weight loss interventions specifically in populations with sleep disorders is limited, and weight management is not yet a mainstay of treatment [15].

New pharmacotherapeutic options for sleep disorders are available to help manage various symptoms that may persist despite primary treatment. As with all pharmacologic treatments, medications used to treat sleep disorders could have positive, negative, or neutral effects on body weight. For instance, some studies suggest that long-term treatment with modafinil or armodafinil can result in weight loss in patients with EDS associated with OSA or narcolepsy [17,18]. In contrast, treatment with pitolisant has been associated with reports of adverse events of weight gain in patients with narcolepsy [19]. Solriamfetol is a dopamine/norepinephrine reuptake inhibitor approved in the United States and European Union to improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with OSA (37.5–150 mg/day) or narcolepsy (75–150 mg/day) [20,21]. In clinical trials of solriamfetol, decreased appetite was a common adverse event, but it was unknown how solriamfetol impacted body weight [22,23]. The current analysis evaluated changes in weight in participants with narcolepsy or OSA treated with solriamfetol in clinical trials. We sought to test the hypothesis that solriamfetol use may be associated with weight loss in a dose-dependent manner, using data from phase 3 trials.

2. Methods

2.1. Study design

To characterize shorter-term changes in weight during solriamfetol treatment, data were analyzed from two 12-week, randomized, double-blind, placebo-controlled, phase 3 clinical trials. To characterize longer-term changes in weight during solriamfetol treatment, data were analyzed from an open-label extension phase 3 clinical trial up to 52 weeks in duration. Detailed study methods have been published previously, with results of the primary analyses [22–24], and are briefly summarized below. All studies were approved by institutional review boards or ethics committees at each institution and were performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Participants

For the shorter-term studies, one study enrolled adults (18–75 years) with EDS associated with OSA and one study enrolled adults (18–75 years) with narcolepsy. Participants with OSA or narcolepsy who had previously completed one of several clinical trials of solriamfetol were eligible for enrollment in the longer-term open-label extension trial [22,23,25–27]. Results are presented for participants who enrolled in the open-label extension immediately after completion of 1 of the 12-week, phase 3 studies [22,23].

For the shorter- and longer-term studies, inclusion criteria included Epworth Sleepiness Scale score $\geq$10 (shorter-term studies only), a usual nightly sleep duration of at least 6 h, and BMI of 18 to <45 kg/m^2. Participants were excluded if they had a usual bedtime later than 1 a.m. or occupation requiring nighttime or variable shiftwork. For the longer-term study, participants were excluded if they experienced any solriamfetol-related serious adverse event (AE) or any AE in a previous trial that may have prevented safe participation in the current trial.

2.3. Treatment

In the shorter-term studies, participants with OSA were randomized 1:1:2:2:2 to 37.5 mg, 75 mg, 150 mg, or 300 mg of solriamfetol or placebo and participants with narcolepsy were randomized 1:1:1:1 to 75 mg, 150 mg, or 300 mg of solriamfetol or placebo. In the longer-term study, open-label solriamfetol treatment was initiated for all participants at 75 mg/day during a 2-week titration phase, during which participants were titrated to an efficacious and tolerable dose. During the titration phase, participants could titrate up 1 dose level (to 150 mg/day, followed by a maximum dose of 300 mg/day) every 3 days; participants could titrate down (to 75 or 150 mg/day) at any time. The titration phase was followed by an open-label maintenance phase, during which participants remained on the stable dose reached at the end of the titration phase (75, 150, or 300 mg/day). Open-label treatment had a total duration of 40 weeks (up to 52 total weeks of solriamfetol treatment from baseline of parent study).

2.4. Assessments

Body weight was assessed as part of routine physical examinations and measured at every clinic visit with participants in ordinary indoor clothes without shoes. A qualified investigator (or designee) performed the examinations. Changes in weight were evaluated from baseline to the end of each study. Long-term changes in cardiometabolic risk biomarkers, including serum total cholesterol, triglyceride, and glucose levels, were evaluated from baseline to the end of the open-label extension. Treatment-emergent AEs (TEAEs) were recorded throughout the course of the individual studies by the investigator(s) and coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 18.0; weight-related TEAEs are reported here.

2.5. Statistical analysis

All data were evaluated for participants in the safety population, defined as those who received $\geq$1 dose of study drug. Given the exploratory nature of the analyses, all data were summarized descriptively and presented separately for the shorter-term and longer-term studies. Note that for the longer-term study, baseline was defined as the baseline of the parent study.

3. Results

3.1. Participant population

In the shorter-term studies, a total of 474 participants with OSA and 236 participants with narcolepsy were included in the safety populations. In the longer-term study, a total of 519 participants (OSA, n = 333; narcolepsy, n = 186) were included in the safety population. Across studies and treatment groups (placebo or combined solriamfetol), the mean age ranged from 36.0 to 55.1 years, 32.8%–64.7% of participants were male, and mean BMI ranged from 28.0 to 33.5 kg/m^2 (Table 1 [full demographics and baseline clinical characteristics have been reported previously]) [22–24]. At baseline, participants with OSA had higher weight and BMI compared with participants with narcolepsy (Table 1).

3.2. Changes in body weight

For participants with OSA in the shorter-term study, median (interquartile range [IQR]) percent change in weight from baseline to week 12 decreased across all solriamfetol doses (−0.84% [−3.12 to 0.53]) and increased with placebo (0.54% [−0.66 to 1.98]) (Fig. 1A). For participants with narcolepsy in the shorter-term study, median (IQR) percent change in weight from baseline to week 12 decreased across all solriamfetol doses (−0.07% [−2.04 to 0.84]) and increased with placebo (3.08% [0.84 to 5.55]) (Fig. 1B).

At week 12, 11.5% of solriamfetol-treated participants with OSA and 7.7% of solriamfetol-treated participants with narcolepsy had ≥5% weight decrease relative to baseline, compared with 6.9% and 0% of participants on placebo, respectively (Fig. 2A and Fig. 2B). Weight increases ≥5% at week 12 were observed for 2.0% of solriamfetol-treated participants with OSA and 4.9% of solriamfetol-treated participants with narcolepsy, compared with 5.9% and 30.8% on placebo, respectively.

In the longer-term study (OSA and narcolepsy combined), median (IQR) percent change in weight from baseline of the parent study to week 40 of the open-label extension across all solriamfetol doses was −1.76% (−5.4 to 1.6) (Fig. 3A). Changes in weight showed a dose-dependent pattern, such that the greatest decreases in weight occurred with higher doses of solriamfetol (Fig. 3A). Weight changes in subgroups of participants with OSA or narcolepsy showed a similar pattern, with overall median (IQR) percent changes in weight of −2.2% (−5.6 to 0.7) and 1.1% (−4.4 to 2.7), respectively (Fig. 3B and Fig. 3C).

At the end of the longer-term study, 25.7% of participants had ≥5% weight loss relative to baseline of the parent study (Fig. 4A). The percentage of participants with weight loss ≥5% relative to baseline also increased in a dose-dependent manner (4.5%, 17.3%, and 32.4% of participants on solriamfetol 75, 150, and 300 mg, respectively) (Fig. 4A). Similar results were found among subgroups of participants with OSA or narcolepsy, with 26.4% and 24.2% of participants experiencing weight loss ≥5%, respectively (Fig. 4B and Fig. 4C). Thirty-four (9.1%) participants had ≥5% weight gain (75 mg, n = 3; 150 mg, n = 13; 300 mg, n = 18).

3.3. Total cholesterol, triglyceride, and glucose levels

In the longer-term study (OSA and narcolepsy combined), participants showed small mean (SD) changes in total cholesterol (−0.0 [0.7] mmol/L), triglycerides (−0.1 [0.9] mmol/L), and glucose levels (0.1 [1.4] mmol/L) from baseline of parent study to week 40 of the open-label extension. In the subgroup of participants with narcolepsy, the mean (SD) change in total cholesterol was −0.1 (0.6) mmol/L, in triglycerides was −0.1 (0.8) mmol/L, and in glucose levels 0.2 (0.8) mmol/L. In the subgroup of participants with OSA, the mean (SD) change in total cholesterol was 0.0 (0.7) mmol/L, in triglycerides was −0.0 (0.9), and in glucose levels was 0.1 (1.6) mmol/L.

3.4. Adverse events

Weight-related TEAEs are summarized in Table 2 and Table 3 (full information on TEAEs has been reported previously) [22–24]. No weight-related TEAEs were serious. During the longer-term study, decreased appetite led to study discontinuation in 2 participants (1 [0.3%] with OSA on 300 mg and 1 [0.5%] with narcolepsy on 150 mg) and reduction of study drug dose in 5 (0.8%) participants with narcolepsy. Decreased weight did not lead to study discontinuation or reduction of study drug dose in any participants.

4. Discussion

Findings from the current analysis provide several important contributions to the literature. After shorter-term (12 weeks) solriamfetol treatment, there were dose-related reductions in weight (median percent changes) in participants with OSA and minimal or no changes in weight in participants with narcolepsy across solriamfetol treatment groups, whereas there were increases in the placebo groups. After longer-term (up to 52 weeks) solriamfetol treatment, 25.7% (96/374) of participants with OSA or narcolepsy experienced ≥5% weight loss relative to baseline. Notably, these changes were observed in participants who, on average, had high BMIs and were considered to be overweight or obese at baseline (mean BMI between 28 and 33 kg/m^2) [28].

In the current analysis, participants showed small changes in blood serum chemistry parameters, including total cholesterol, glucose, and triglyceride levels, during longer-term treatment. Future studies are needed to determine whether weight loss related to solriamfetol treatment is indeed associated with concomitant improvements in cardiometabolic risk factors.

The mechanisms underlying how solriamfetol might lead to

Table 1
Demographics and baseline characteristics (safety population).

	Shorter-term RCT OSA		Shorter-term RCT Narcolepsy		Longer-term OLE		
	Placebo	Combined solriamfetol	Placebo	Combined solriamfetol	Overall	OSA	Narcolepsy
n	119	355	59	177	519	333	186
Age, mean (SD), years	54.1 (11.4)	53.9 (10.8)	36.0 (15.2)	36.3 (12.5)	48.4 (14.4)	54.6 (10.8)	37.2 (13.3)
Sex, n (%) male	77 (64.7)	220 (62.0)	24 (40.7)	58 (32.8)	267 (51.4)	203 (61.0)	64 (34.4)
Race, n (%) white	87 (73.1)	274 (77.2)	47 (79.7)	142 (80.2)	409 (78.8)	260 (78.1)	149 (80.1)
BMI, mean (SD), kg/m^2	33.1 (5.2)	33.3 (5.3)	29.1 (6.0)	28 (5.8)	31.8 (6.0)	33.6 (5.2)	28.5 (5.9)
Weight, median (range), kg	99.7 (50.5, 157.1)	98.4 (52.4, 153.3)	82.3 (52.0, 130.0)	79.3 (45.4, 141.1)	93.4 (45.4, 157.1)	98.9 (50.5, 157.1)	82.0 (45.4, 141.1)

BMI, body mass index; OLE, open-label extension; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SD, standard deviation.

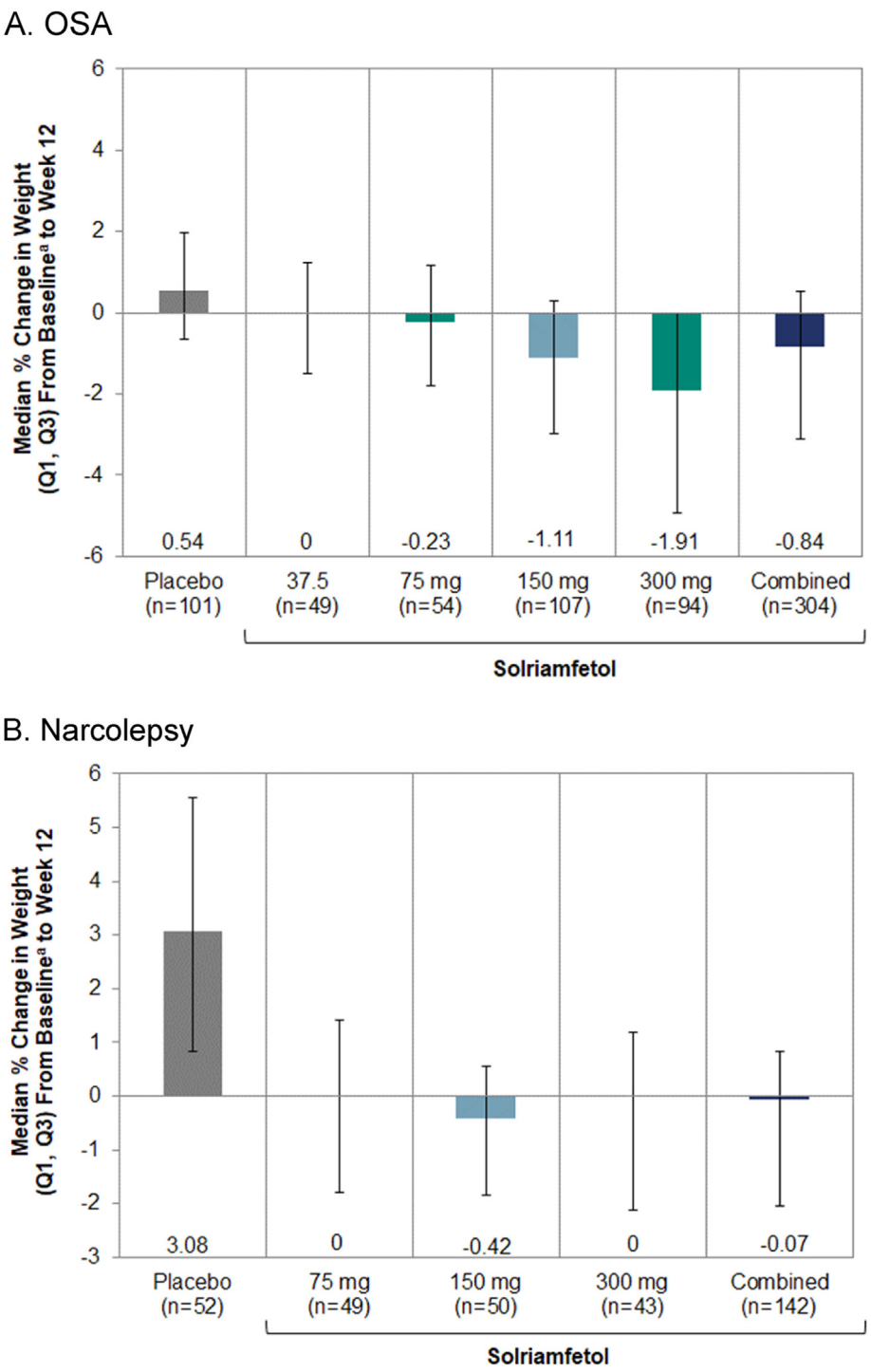

Fig. 1. Shorter-term RCT studies: median percent changes in weight with solriamfetol treatment from baseline to week 12.
OSA, obstructive sleep apnea; RCT, randomized controlled trial.

weight loss in some participants must map to either energy intake or expenditure, or both. Previous studies have shown that bupropion, another dopamine and norepinephrine reuptake inhibitor [29], is associated with weight loss in overweight and obese patients. It has been postulated that bupropion's weight loss effects could be mediated by its action on the dopaminergic reward system, thereby leading to improvements in control of eating and response to food cravings [30–32]. In the current study, some reduced appetite was observed in a subset of participants on solriamfetol; however, caloric expenditure has not been systematically assessed in this context or with alerting agents in general. The percent change in body weight decreased with higher doses of solriamfetol, but that does not provide the insight needed to understand cause and effect. Further work is thus required to understand the impact of solriamfetol on energy balance.

Several studies, including meta-analyses, have suggested that CPAP treatment is associated with weight gain in patients with OSA [13,14]. Some have argued that hormonal changes associated with

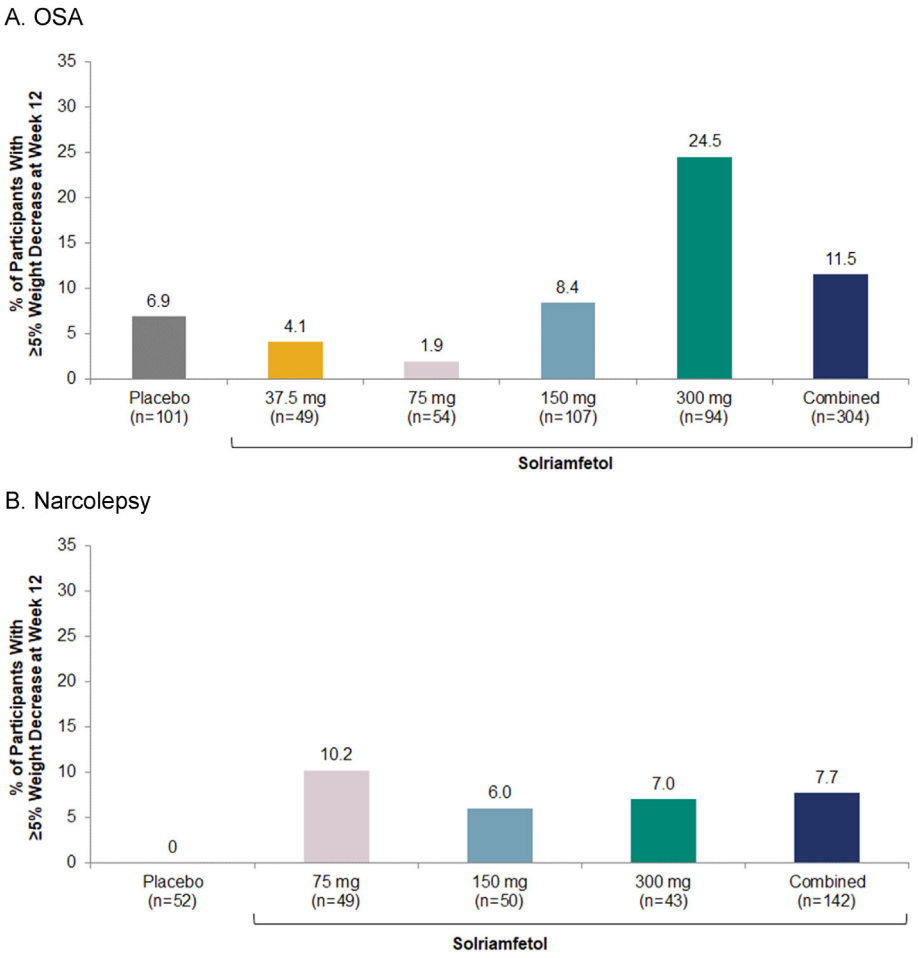

Fig. 2. Shorter-term RCT studies: percentage of participants with ≥5% weight decrease from baseline to week 12.
OSA, obstructive sleep apnea; RCT, randomized controlled trial.

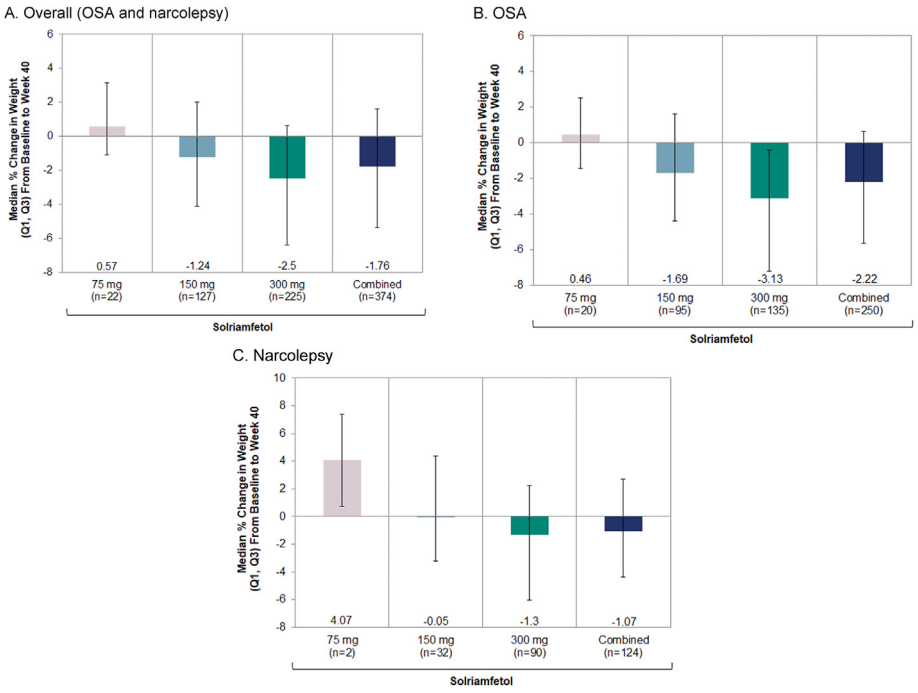

Fig. 3. Longer-term OLE study: median percent changes in weight with solriamfetol treatment from baseline of parent study to week 40.[a]
[a]At week 40 of the OLE, participants had received up to 52 weeks of solriamfetol treatment.
Dose group represents the dose level that the participant received most frequently in the study.
OLE, open-label extension; OSA, obstructive sleep apnea.

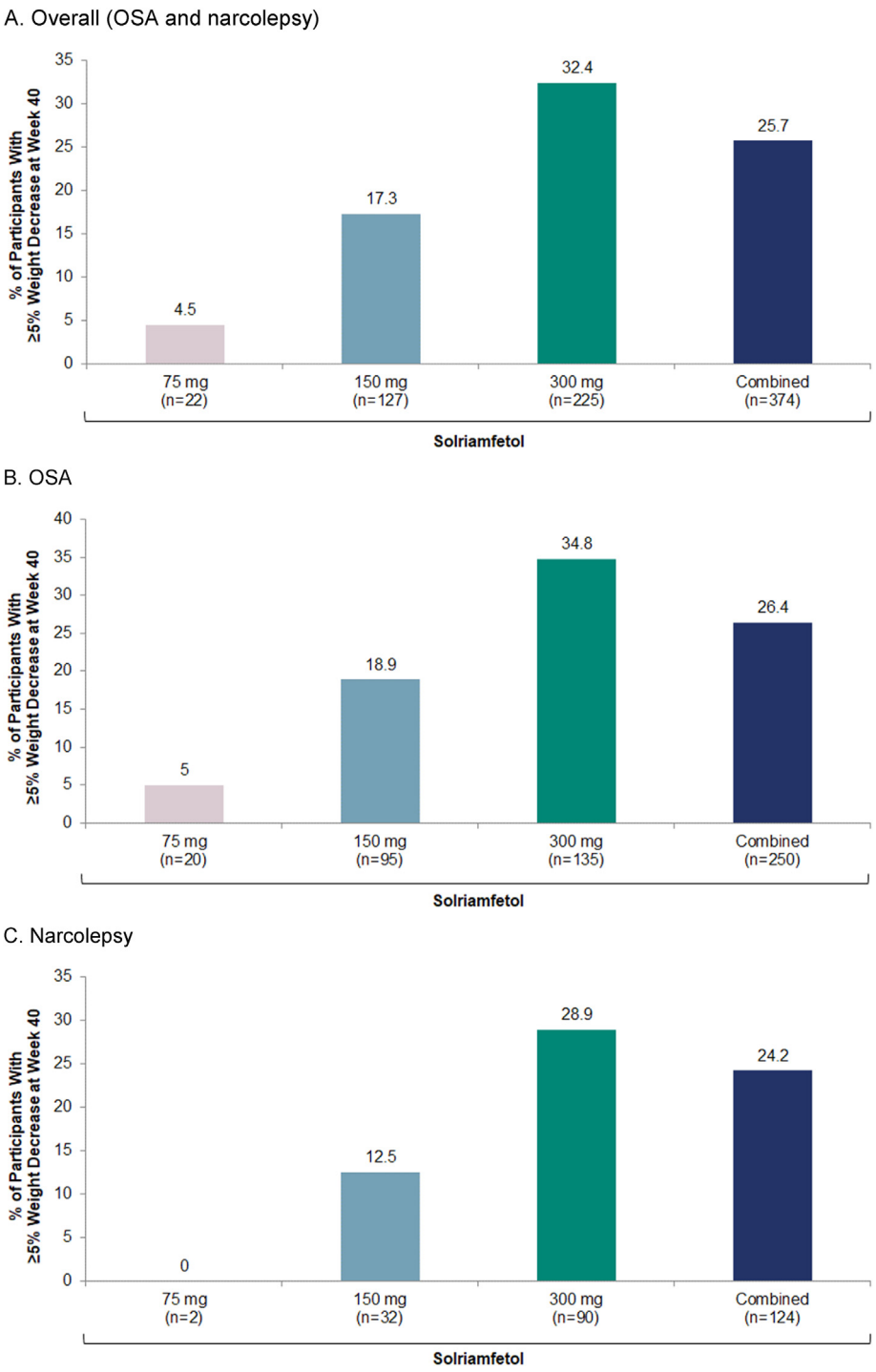

Fig. 4. Longer-term OLE study: percentage of participants with ≥5% weight decrease from baseline of parent study to week 40.[a]
[a]At week 40 of the OLE, participants had received up to 52 weeks of solriamfetol treatment.
Dose group represents the dose level that the participant received most frequently in the study.
OLE, open-label extension; OSA, obstructive sleep apnea.

OSA treatment, for instance sustained slow wave sleep with growth hormone release, may promote weight gain over time [33]. Others have suggested that patients' behaviors change after initiating CPAP. Some patients report "getting their life back" with CPAP treatment, which in many cases involves resuming activities associated with caloric intake (eg, dinner with spouse, beers with friends, etc.). Moreover, some have suggested that a high work of breathing can occur in untreated OSA, such that some patients may struggle to breathe and burn many calories as a result [34]. CPAP initiation may reduce this associated caloric expenditure; as such, marked increases in daytime activity may be required to maintain neutral energy balance [35]. Finally, a recent study has suggested that fluid accumulation (extracellular fluid volume) may develop after CPAP initiation, and increased body weight associated with

Table 2
Shorter-term RCT studies: Weight-related TEAEs.

TEAE, n (%) of Participants	OSA					Narcolepsy			
	Placebo (n = 119)	Solriamfetol				Placebo (n = 59)	Solriamfetol		
		37.5 mg (n = 58)	75 mg (n = 62)	150 mg (n = 117)	300 mg (n = 118)		75 mg (n = 59)	150 mg (n = 59)	300 mg (n = 59)
Decreased appetite	1 (0.8)	1 (1.7)	3 (4.8)	9 (7.7)	14 (11.9)	1 (1.7)	5 (8.5)	5 (8.5)	9 (15.3)
Decreased weight	0	0	0	1 (0.9)	1 (0.8)	0	1 (1.7)	1 (1.7)	3 (5.1)
Increased appetite	0	0	0	0	0	0	1 (1.7)	1 (1.7)	0
Increased weight	0	0	0	0	0	3 (5.1)	2 (3.4)	0	1 (1.7)

OSA, obstructive sleep apnea; RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

Table 3
Longer-term OLE study: Weight-related TEAEs.

TEAE, n (%) of participants	Overall			OSA			Narcolepsy		
	75 mg (n = 46)	150 mg (n = 182)	300 mg (n = 291)	75 mg (n = 36)	150 mg (n = 127)	300 mg (n = 170)	75 mg (n = 10)	150 mg (n = 55)	300 mg (n = 121)
Decreased appetite	0	0	0	0	0	0	0	0	0
Decreased weight	0	2 (1.0)	2 (0.7)	0	2 (1.6)	0	0	0	2 (1.7)
Increased appetite	0	0	0	0	0	0	0	0	0
Increased weight	1 (2.2)	0	2 (0.7)	1 (2.8)	0	1 (0.6)	0	0	1 (0.8)

OLE, open-label extension; TEAE, treatment-emergent adverse event.

CPAP treatment may be related to fluid retention rather than fat accumulation [13]. Regardless of the mechanism underlying CPAP-induced weight gain, these findings underscore the importance of efforts to promote weight loss and to minimize weight gain while addressing treatment of sleep disorders.

The current study has a number of strengths, including its sample size, and clinically relevant health outcomes. However, several limitations are also noted. First, these analyses were exploratory and conducted on existing data. As such, data were only summarized descriptively and no statistical analyses were performed, limiting interpretation of results. Prospective randomized clinical trials that assess the impact of solriamfetol on energy balance would enhance mechanistic insights. Another limitation is the lack of a placebo control group in the longer-term study. In theory, the observed changes in body weight and associated metabolic factors may have been a function of time rather than induced by solriamfetol per se. However, common clinical experience suggests that spontaneous decreases in body weight or cardiometabolic risk are uncommon in patients with sleep disorders. Regardless, future well-controlled studies are needed to corroborate these findings. Further, we acknowledge that these studies were not designed to assess potential effects on major outcomes such as myocardial infarction or stroke; these hard outcomes would likely require a much larger sample size with longer-term follow-up for adequate power. Nonetheless, improvements in surrogate outcomes would be compelling and of interest for future well-designed and well-powered studies. Moreover, we view body weight per se as a clinically important outcome based on patient preferences. It is also important to note that results for a 300 mg dose were included in the current analysis to demonstrate dose-dependent effects; however, the maximum approved dose of solriamfetol in patients with narcolepsy or OSA is 150 mg once daily [20,21]. Despite these limitations, these findings are of clinical interest and may provide a substrate to encourage subsequent research.

5. Conclusions

Many sleep disorders, including OSA and narcolepsy, are associated with obesity and overweight. Solriamfetol was generally associated with decreases in body weight in a dose-related manner. Further research in prospective randomized controlled studies is required to assess the long-term cardiometabolic impact of solriamfetol treatment.

Clinical trial registration

Trial 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.
ID number: NCT02348632.

Funding

This study was supported by Jazz Pharmaceuticals. At the time the study was conducted, Jazz Pharmaceuticals had worldwide development, manufacturing, and commercialization rights to solriamfetol, excluding certain jurisdictions in Asia. Jazz Pharmaceuticals completed the divestiture of Sunosi® (solriamfetol) in the US to Axsome Therapeutics, Inc. on May 9, 2022. SK Biopharmaceuticals, the discoverer of the compound (also known as SKL-N05), maintains rights in 12 Asian markets, including Korea, China, and Japan.

CRediT authorship contribution statement

Atul Malhotra: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Patrick J. Strollo, Jr:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Jean-Louis Pepin:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Paula Schweitzer:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Gert Jan Lammers:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Jan Hedner:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Susan Redline:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Dan Chen:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Patricia Chandler:** Conceptualization, Methodology,

Writing – review & editing. **Shay Bujanover:** Conceptualization, Methodology, Writing – review & editing. **Kingman Strohl:** Conceptualization, Investigation, Methodology, Writing – review & editing.

Declaration of competing interest

A Malhotra has served as a principal investigator for a Jazz study. He is funded by the NIH and reports income related to medical education from Jazz, Livanova, Equillium and Corvus. ResMed gave a philanthropic donation to the University of California, San Diego, in support of a sleep center.

PJ Strollo, Jr has received consultancy fees and honoraria from Inspire Medical Systems, ResMed, Philips-Respironics, Emmi Solutions, Jazz Pharmaceuticals, and Itamar; has received research funding from the National Institutes of Health and Inspire Medical Systems; and has a provisional patent for positive airway pressure with integrated oxygen.

J-L Pepin has received lecture fees or conference traveling grants from Resmed, Perimetre, Philips, Fisher and Paykel, AstraZeneca, Jazz Pharmaceuticals, Agiradom, and Teva, and has received unrestricted research funding from ResMed, Philips, GlaxoSmithKline, Bioprojet, Fondation de la Recherche Medicale (Foundation for Medical Research), Direction de la Recherche Clinique du CHU de Grenoble (Research Branch Clinic CHU de Grenoble), and fond de dotation “Agir pour les Maladies Chroniques” (endowment fund “Acting for Chronic Diseases”).

P Schweitzer has received consultancy fees from Jazz Pharmaceuticals and Apnimed. Her institution has received research funding from Apnimed, Avadel, Jazz Pharmaceuticals, Inspire Medical Systems, and Suven Life Sciences.

GJ Lammers has received consultancy fees and/or honoraria and has been a speakers’ bureau member and/or an advisory board participant for UCB Pharma, Bioprojet, Theranexus, and Jazz Pharmaceuticals.

J Hedner has served on the speakers’ bureaus for AstraZeneca, Philips Respironics, Itamar Medical, and BresoTec, and serves as a board member for Cereus Pharma.

S Redline: has received grant support and consulting fees from Jazz Pharma as well as consulting fees from Eisai Inc, Eli Lilly Inc, and Respicardia Inc.

D Chen and **P Chandler** are employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc.

S Bujanover is a former employee of Jazz Pharmaceuticals who, in the course of this employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc.

K Strohl has served as an advisory board member and is a principal investigator for Jazz; is a site principal investigator for Inspire Medical Systems; and has received consultancy fees from Sommetrics, GSK (Galvani Bioelectronics), and Seven Dreamers.

Acknowledgments

A Malhotra wrote the first draft of the manuscript. Under the direction of the authors, Hannah K. Ritchie, PhD, and Jim Wood of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support for this article, which was funded by Jazz Pharmaceuticals and Axsome Therapeutics, Inc.

References

[1] Watson NF, Badr MS, Belenky G, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep 2015;38(6):843–4.
[2] Markwald RR, Melanson EL, Smith MR, et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc Natl Acad Sci U S A 2013;110(14):5695–700.
[3] Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1(3):e62.
[4] Bjorvatn B, Sagen IM, Øyane N, et al. The association between sleep duration, body mass index and metabolic measures in the Hordaland Health Study. J Sleep Res 2007;16(1):66–76.
[5] Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 2008;31(5):619–26.
[6] Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Prim 2015;1:15015.
[7] Sonka K, Kemlink D, Buskova J, et al. Obesity accompanies narcolepsy with cataplexy but not narcolepsy without cataplexy. Neuroendocrinol Lett 2010;31(5):631–4.
[8] Dahmen N, Bierbrauer J, Kasten M. Increased prevalence of obesity in narcoleptic patients and relatives. Eur Arch Psychiatr Clin Neurosci 2001;251(2):85–9.
[9] Kok SW, Overeem S, Visscher TL, et al. Hypocretin deficiency in narcoleptic humans is associated with abdominal obesity. Obes Res 2003;11(9):1147–54.
[10] McNicholas WT, Bonsignore MR, Lévy P, Ryan S. Mild obstructive sleep apnoea: clinical relevance and approaches to management. Lancet Respir Med 2016;4(10):826–34.
[11] Sellayah D, Bharaj P, Sikder D. Orexin is required for brown adipose tissue development, differentiation, and function. Cell Metabol 2011;14(4):478–90.
[12] Hara J, Beuckmann CT, Nambu T, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron 2001;30(2):345–54.
[13] Herculano S, Grad GF, Drager LF, et al. Weight gain induced by continuous positive airway pressure in patients with obstructive sleep apnea is mediated by fluid accumulation: a randomized cross-over controlled trial. Am J Respir Crit Care Med 2021;203(1):134–6.
[14] Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM, Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. Thorax 2015;70(3):258–64.
[15] Hudgel DW, Patel SR, Ahasic AM, et al. The role of weight management in the treatment of adult obstructive sleep apnea. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2018;198(6):e70–87.
[16] Chirinos JA, Gurubhagavatula I, Teff K, et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med 2014;370(24):2265–75.
[17] Chapman JL, Cayanan EA, Hoyos CM, et al. Does armodafinil improve driving task performance and weight loss in sleep apnea? A randomized trial. Am J Respir Crit Care Med 2018;198(7):941–50.
[18] Roth T, Schwartz JR, Hirshkowitz M, Erman MK, Dayno JM, Arora S. Evaluation of the safety of modafinil for treatment of excessive sleepiness. J Clin Sleep Med 2007;3(6):595–602.
[19] Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III study. Sleep 2019;42(11).
[20] Sunosi™ (solriamfetol) tablets prescribing information. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2021.
[21] Sunosi™ (solriamfetol) tablets summary of product characteristics. Dublin, Ireland: Jazz Pharmaceuticals Ireland Ltd; 2020.
[22] Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. Am J Respir Crit Care Med 2019;199(11):1421–31.
[23] Thorpy MJ, Shapiro C, Mayer G, et al. A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol 2019;85(3):359–70.
[24] 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.
[25] Bogan RK, Feldman N, Emsellem HA, et al. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. Sleep Med 2015;16(9):1102–8.
[26] Ruoff C, Swick TJ, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. Sleep 2016;39(7):1379–87.
[27] Strollo Jr PJ, Hedner J, Collop N, et al. Solriamfetol for the treatment of excessive sleepiness in OSA: a placebo-controlled randomized withdrawal study. Chest 2019;155(2):364–74.
[28] About Adult BMI. Centers for disease control and prevention. https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html. [Accessed 7 September 2021].
[29] Wellbutrin [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
[30] Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376(9741):595–605.
[31] Mullally JA, Chung WK, LeDuc CA, et al. Weight-loss response to naltrexone/bupropion is modulated by the Taq1A genetic variant near DRD2 (rs1800497):

a pilot study. Diabetes Obes Metabol 2021;23(3):850–3.
[32] Billes SK, Sinnayah P, Cowley MA. Naltrexone/bupropion for obesity: an investigational combination pharmacotherapy for weight loss. Pharmacol Res 2014;84:1–11.
[33] Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C, Follenius M. Continuous positive airway pressure treatment. Effects on growth hormone, insulin and glucose profiles in obstructive sleep apnea patients. Horm Metab Res 1993;25(7):375–81.
[34] Shechter A. Obstructive sleep apnea and energy balance regulation: a systematic review. Sleep Med Rev 2017;34:59–69.
[35] Tachikawa R, Ikeda K, Minami T, et al. Changes in energy metabolism after continuous positive airway pressure for obstructive sleep apnea. Am J Respir Crit Care Med 2016;194(6):729–38.