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Authors

Rosenberg, Russell
Thorpy, Michael J
Dauvilliers, Yves
et al.

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SCIENTIFIC INVESTIGATIONS

Incidence and duration of common early-onset adverse events in randomized controlled trials of solriamfetol for treatment of excessive daytime sleepiness in obstructive sleep apnea and narcolepsy

Russell Rosenberg, PhD[1]; Michael J. Thorpy, MD[2]; Yves Dauvilliers, MD, PhD[3]; Paula K. Schweitzer, PhD[4]; Gary Zammit, PhD[5,6]; Mark Gotfried, MD[7]; Shay Bujanover, MD[8]; Brian Scheckner, PharmD, BCPP, CMPP[9]; Atul Malhotra, MD[10]

[1]NeuroTrials Research, Inc, Atlanta, Georgia; [2]Montefiore Medical Center, Bronx, New York; [3]Sleep Unit, Department of Neurology, Gui-de-Chauliac Hospital, CHU Montpellier, INSERM, Montpellier, France; [4]Sleep Medicine and Research Center, St Luke's Hospital, Chesterfield, Missouri; [5]Clinilabs Drug Development Corporation, New York, New York; [6]Icahn School of Medicine at Mount Sinai, New York, New York; [7]Pulmonary Associates, PA, Phoenix, Arizona; [8]Jazz Pharmaceuticals, Palo Alto, California; [9]Jazz Pharmaceuticals, Philadelphia, Pennsylvania; [10]University of California, San Diego, San Diego, California

Study Objectives: This post hoc analysis characterized the weekly incidence and overall duration of common early-onset, treatment-emergent adverse events (TEAEs) during solriamfetol treatment.

Methods: Participants (obstructive sleep apnea [OSA], n = 474; narcolepsy, n = 236) were randomized to 12 weeks of placebo or solriamfetol 37.5 (OSA only), 75, 150, or 300 mg. For common early-onset TEAEs (those occurring in ≥ 5% of participants in any solriamfetol dose group and with a higher incidence than that observed in placebo-treated participants during week 1), the incidence of new occurrence or change in severity over time was calculated for each subsequent study week. Data were analyzed separately for each study and summarized by placebo and combined solriamfetol groups.

Results: Common early-onset TEAEs (at doses ≤ 150 mg; ie, approved doses) included headache (OSA, 5.1%; narcolepsy, 8.5%), nausea (OSA, 2.5%; narcolepsy, 4.2%), decreased appetite (OSA, 4.2%; narcolepsy, 5.9%), as well as anxiety (2.1%), insomnia (1.3%), and feeling jittery (3.0%) in OSA and dry mouth (4.2%) in narcolepsy. Incidence of common early-onset TEAEs was highest at week 1 and decreased over time. In OSA at doses ≤ 150 mg, headache, nausea, and feeling jittery had median durations ≤ 8 days, whereas decreased appetite, anxiety, and insomnia had longer durations. In narcolepsy at doses ≤ 150 mg, headache and nausea had median durations ≤ 8 days, whereas decreased appetite and dry mouth had longer durations. Most TEAEs were mild to moderate in severity.

Conclusions: Common early-onset TEAEs with solriamfetol are limited in duration, with the majority subsiding during the first week of treatment.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Twelve-week Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in Narcolepsy; URL: https://clinicaltrials.gov/ct2/show/NCT02348593; Identifier: NCT02348593; and Name: Twelve-week Study of the Safety and Efficacy of JZP-110 in the Treatment of Excessive Sleepiness in OSA; URL: https://clinicaltrials.gov/ct2/show/NCT02348606; Identifier: NCT02348606

Keywords: solriamfetol, Sunosi, JZP-110, safety, sleep, apnea, lung, narcolepsy, OSA

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The most common treatment-emergent adverse events associated with solriamfetol treatment have been reported; however, how these adverse events may evolve over time has not been well characterized. Characterizing the adverse-event profile will help set expectations for patients and prescribing physicians.

Study Impact: Common early-onset, treatment-emergent adverse events identified during week 1 of solriamfetol treatment included headache, nausea, decreased appetite, anxiety (obstructive sleep apnea only), insomnia (obstructive sleep apnea only), feeling jittery (obstructive sleep apnea only), and dry mouth (narcolepsy only). Prescribing physicians can inform patients that certain adverse events with solriamfetol such as headache, nausea, and feeling jittery are limited in duration while others such as decreased appetite, anxiety, insomnia, and dry mouth may persist for a longer duration.

INTRODUCTION

Obstructive sleep apnea (OSA) and narcolepsy are sleep disorders with major adverse sequelae. OSA has been estimated to affect up to 1 billion people worldwide, whereas narcolepsy is considerably less common, with an estimated prevalence of 30.6 to 56.3 per 100,000.[1–3] While narcolepsy and OSA are phenotypically distinct, excessive daytime sleepiness (EDS) is a symptom of both; EDS is associated with impaired function and diminished quality of life.[4–9] Existing treatments for OSA and narcolepsy are helpful but do not resolve EDS in all cases, justifying the implementation of complementary or alternative therapies.

With regard to narcolepsy, various agents are available, including wake-promoting agents, stimulants, and sodium oxybate.[10–15] However, many patients receive polypharmacy[16] and few report complete elimination of symptoms. The treatment of choice for OSA is nasal continuous positive airway pressure

(CPAP).[17] Nasal CPAP therapy has excellent efficacy in treating the underlying airway obstruction. However, OSA severity based on the apnea-hypopnea index is only loosely predictive of the degree of daytime sleepiness, and CPAP effectiveness is variable due to adherence issues in some patients.[18] In general, CPAP adherence is predictive of the degree of improvement in EDS.[19,20] However, even among adherent CPAP-treated patients, an estimated 9–22% of patients continue to experience residual EDS.[19,21] Even with optimal CPAP adherence and control of other factors that might contribute to sleepiness, some patients do not have elimination of symptoms, suggesting that residual EDS may warrant symptomatic treatment independent from the underlying airway obstruction.[20]

Solriamfetol (Sunosi; Jazz Pharmaceuticals, Palo Alto, CA) is a dopamine and norepinephrine reuptake inhibitor approved in the United States and European Union for the treatment of EDS in adults with OSA (37.5–150 mg/d) or narcolepsy (75–150 mg/d).[22,23] The safety and efficacy of solriamfetol in reducing EDS and improving wakefulness have been demonstrated in a number of short-term randomized controlled trials in participants with OSA[24,25] and those with narcolepsy.[26] In addition, a long-term (up to 1 year) open-label extension trial showed sustained benefits with ongoing therapy.[27] However, as with most medical therapies, pharmacological treatments have both risks as well as benefits. The most common treatment-emergent adverse events (TEAEs) associated with solriamfetol treatment in 12-week studies were headache, nausea, decreased appetite, nasopharyngitis, dry mouth, insomnia, and anxiety, with a similar safety profile observed in the long-term study.[24,26,27] Although previous publications[24,26,27] have reported the overall incidence and severity of the most common TEAEs experienced with solriamfetol treatment, to date, how these TEAEs may evolve over time has not been well characterized (eg, time of onset, duration, etc). Characterizing the side-effect profile of these medications, particularly TEAEs that occur at the onset of treatment, is clinically important in order to set expectations for patients and prescribing physicians. Informed expectations regarding potential TEAEs at the start of solriamfetol treatment and their duration will help clinicians optimize therapy in patients.

On the basis of this conceptual framework, the objective of the current analysis was to characterize the weekly incidence and overall duration of common early-onset TEAEs associated with solriamfetol treatment in randomized, placebo-controlled studies of participants with narcolepsy or EDS associated with OSA. The hypothesis was that the side effects of solriamfetol treatment that appear following drug initiation would dissipate relatively quickly, and mostly would not reappear later during treatment, as evidenced by the safety profile from the 12-month, open-label study.[27]

METHODS

Study design

This post hoc analysis included data from the Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) program. TONES 2[26] and TONES 3[24] were two 12-week, randomized, double-blind, placebo-controlled phase 3 trials that evaluated the safety and efficacy of solriamfetol in treating EDS in adults with narcolepsy or OSA, respectively. Both 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. Full details of the study methods have been reported in the primary publications,[24,26] and are briefly summarized below.

Participants

Eligible participants were adults (aged 18–75 years) diagnosed with narcolepsy or OSA, according to *International Classification of Sleep Disorders,* third edition (ICSD-3), or *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5), criteria, with baseline Epworth Sleepiness Scale (ESS) scores ≥ 10. In addition, participants had baseline Maintenance of Wakefulness Test (MWT) mean sleep latencies < 25 (narcolepsy) or < 30 (OSA) minutes, usual nightly sleep duration ≥ 6 hours, and, for participants with OSA, at least minimal, stable use of or had attempted to use a primary OSA therapy (CPAP, oral appliance, or surgical intervention). Participants were excluded if they had a usual bedtime later than 1:00 AM, occupation requiring nighttime or variable shift work, or any other clinically relevant medical, behavioral, or psychiatric disorders associated with EDS.

Treatment

Participants with narcolepsy were randomly assigned (1:1:1:1) to 12 weeks of treatment with placebo or solriamfetol 75, 150, or 300 mg once daily. Participants with OSA were randomly assigned (2:1:1:2:2) to 12 weeks of treatment with placebo or solriamfetol 37.5, 75, 150, or 300 mg once daily. Participants randomized to receive 150 mg initially received 75 mg during a 3-day titration phase prior to being titrated up to 150 mg. Likewise, participants randomized to receive 300 mg initially received 150 mg for 3 days prior to being titrated up to 300 mg.

Assessment of adverse events

All adverse events (AEs), whether observed by the investigator, reported by the participant, or determined by laboratory tests, that occurred from the time written informed consent was obtained until the final study visit or early termination, were documented. An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, regardless of whether it was considered related to the study drug or procedure. A TEAE was defined as an AE that either began or worsened after the first dose of study drug. For each event, signs/symptoms, date of onset and resolution (duration), severity (mild, moderate, or severe), seriousness, relationship to study drug or procedure, and action taken were collected.

Statistical analysis

Common early-onset TEAEs, defined as those occurring in ≥ 5% of participants in any solriamfetol dose group and more frequently in solriamfetol-treated participants than placebo during week 1,[28] were the AEs of interest for the current analysis.

Table 1—Demographic and baseline clinical characteristics.

	OSA		Narcolepsy	
	Placebo (n = 119)	Combined Solriamfetol (All Doses) (n = 355)	Placebo (n = 59)	Combined Solriamfetol (All Doses) (n = 177)
Age, mean (SD), y	54.1 (11.4)	53.9 (10.8)	36.0 (15.2)	36.3 (12.5)
Sex, n (%)				
Male	77 (64.7)	220 (62.0)	24 (40.7)	58 (32.8)
Female	42 (35.3)	135 (38.0)	35 (59.3)	119 (67.2)
Body mass index, mean (SD), kg/m^2	33.1 (5.2)	33.3 (5.3)	29.1 (6.0)	28.0 (5.8)
Race, n (%)				
White	87 (73.1)	274 (77.2)	47 (80.0)	142 (80.2)
Black	26 (21.8)	63 (17.7)	10 (16.9)	23 (13.0)
Other	6 (5.0)	18 (5.1)	2 (3.4)	12 (6.8)
MWT sleep latency, mean (SD),[a] min	12.4 (7.2)	12.6 (7.4)	6.1 (5.6)	8.0 (5.7)
ESS score, mean (SD)	15.6 (3.3)	15.1 (3.3)	17.3 (2.8)	17.1 (3.3)

Data are reported for the safety population. [a]For baseline mean sleep latency on MWT, OSA placebo, n = 114; OSA solriamfetol, n = 348; narcolepsy placebo, n = 58; narcolepsy solriamfetol, n = 174. ESS = Epworth Sleepiness Scale, MWT = Maintenance of Wakefulness Test, OSA = obstructive sleep apnea.

TEAEs that met these criteria were assessed for time course, severity, and duration. For common early-onset TEAEs identified during week 1, incidence of new occurrence or worsening in severity over time was calculated for each subsequent study week; increases in severity were counted as a new incidence.[28] Severity was assessed by classifying TEAEs as mild (symptom[s] barely noticeable to participant, does not make participant uncomfortable or influence performance/functioning, and prescription drug not ordinarily needed for relief of symptom[s]), moderate (symptom[s] of sufficient severity to make participant uncomfortable, influences performance of daily activities, and treatment for symptom[s] may be needed), or severe (symptom[s] causes severe discomfort, incapacitates, or significantly affects participant's daily life, treatment for symptom[s] may be given, and/or participant hospitalized). Duration was calculated as the total number of days over the treatment-emergent period that a participant experienced a given TEAE. Consecutive TEAEs differing only in severity were combined for analyses of duration. If there was a gap in time for the same TEAE in a participant, then the TEAE would be considered a new TEAE in the duration calculation.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) system (version 18.0) to classify events by primary system organ class and preferred term. All data were analyzed separately for each study (ie, by disease state). Analyses were based on the safety populations, defined as participants who received ≥ 1 dose of study drug. Baseline demographic and clinical characteristics were summarized descriptively for the placebo and combined solriamfetol (all doses) groups. Incidence and duration of common early-onset TEAEs (either new or of increased severity) were summarized descriptively for the placebo group, individual solriamfetol dose groups, combined solriamfetol group (all doses), and a combined solriamfetol group that included doses ≤ 150 mg (ie, the dose range approved by the US Food and Drug Administration and European Medicines Agency).[22,23] The frequency of discontinuations due to common early-onset TEAEs was also reported.

RESULTS

Participant population

A total of 239 participants with narcolepsy and 476 participants with OSA were randomized in the TONES 2 and TONES 3 studies, respectively. Of these, 236 (98.7%) participants with narcolepsy and 474 (99.6%) participants with OSA were included in the safety populations (**Table 1**). A total of 195 (81.6%) participants with narcolepsy and 404 (84.9%) with OSA completed the respective studies.

Participants with narcolepsy were predominantly female, whereas participants with OSA were predominantly male (**Table 1**). In addition, participants with narcolepsy were younger, had lower body mass index, and had more severe EDS at baseline (ie, higher ESS scores and lower MWT sleep latency) than participants with OSA. Demographics and baseline clinical characteristics were similar in the placebo and combined solriamfetol groups for both participants with OSA and those with narcolepsy (**Table 1**).

Incidence of common early-onset TEAEs over time

Common early-onset TEAEs identified during week 1 (doses ≤ 150 mg) that were similar between disease states included headache (OSA, 5.1%; narcolepsy, 8.5%), nausea (OSA, 2.5%; narcolepsy, 4.2%), and decreased appetite (OSA, 4.2%; narcolepsy, 5.9%) (**Table 2**). Additional common early-onset TEAEs

(doses ≤ 150 mg) in participants with OSA included anxiety (2.1%), insomnia (1.3%), and feeling jittery (3.0%), whereas additional common early-onset TEAEs (doses ≤ 150 mg) in participants with narcolepsy included dry mouth (4.2%). In both participants with OSA and participants with narcolepsy, the incidence of common early-onset TEAEs was highest at week 1 and decreased over time (**Figure 1**, **Figure 2**). At week 12, only headache (OSA, 0%; narcolepsy, 1.3%), nausea (OSA, 0.5%; narcolepsy, 0%), and anxiety (OSA, 0.5%; narcolepsy, 0%) were reported. In general, rates were higher in participants with narcolepsy than in participants with OSA, and incidence was highest with the 300-mg dose.

Most common early-onset TEAEs were mild to moderate in severity. Among participants with OSA, a total of 5 common early-onset TEAEs were severe: 4 reported by solriamfetol-treated participants (week 1: headache, n = 1 [0.3% of combined solriamfetol group; solriamfetol 300 mg]; week 2: nausea, n = 1 [0.3%; solriamfetol 75 mg], and anxiety, n = 2 [0.6%; solriamfetol 150 mg and 300 mg]) and 1 reported by a placebo-treated participant (week 7: headache, n = 1 [0.9%]). Among participants with narcolepsy, a total of 3 common early-onset TEAEs were severe, all reported by solriamfetol-treated participants (week 3: headache, n = 1 [0.6%; solriamfetol 300 mg] and nausea, n = 1 [0.6%; solriamfetol 300 mg]; week 5: headache, n = 1 [0.6%; solriamfetol 150 mg]). In both studies, all other common early-onset TEAEs were considered mild or moderate in severity.

Only 1 common early-onset TEAE was considered to be a preexisting TEAE that increased in severity (headache in a participant with OSA in the 300-mg dose group increased from mild at week 2 to moderate at week 12); all other common early-onset TEAEs in both studies were considered new incidences. There were no deaths in either study.

Duration of common early-onset TEAEs

In participants with OSA receiving approved doses (≤ 150 mg), feeling jittery had a median duration of 4 days and headache and nausea had a median duration of 8 days, whereas decreased appetite, insomnia, and anxiety had longer durations of 18, 21, and 36 days, respectively (**Table 3**). In participants with narcolepsy receiving approved doses (≤ 150 mg), headache and nausea had median durations of 2 and 5 days, respectively, whereas deceased appetite and dry mouth had longer durations of 80 and 82 days, respectively.

Discontinuations due to common early-onset TEAEs

In participants with OSA, a total of 25 participants (7.0%) receiving solriamfetol had any TEAE leading to study drug discontinuation compared with 4 (3.4%) receiving placebo. Among the 25 solriamfetol-treated participants with TEAE-related discontinuations, 11 (44.0%) were due to common early-onset TEAEs and all occurred between weeks 3 through 9. Anxiety (n = 4; 1.1%) and feeling jittery (n = 4; 1.1%) were the common early-onset TEAEs that most frequently led to discontinuation, followed by nausea (n = 3; 0.8%), decreased appetite (n = 1; 0.3%), and insomnia (n = 1; 0.3%). The remaining TEAE-related discontinuations among solriamfetol-treated participants were related to other TEAEs, most of which were reported for 1 participant each. Those reported in ≥ 2 participants were chest discomfort (n = 3), dizziness (n = 3), agitation, restlessness, and tic (n = 2 each). Among placebo-treated participants with TEAE-related discontinuations, none were due to common early-onset TEAEs.

In participants with narcolepsy, 9 participants (5.1%) receiving solriamfetol had any TEAE leading to study drug discontinuation compared with 1 (1.7%) receiving placebo. Among the 9 solriamfetol-treated participants with TEAE-related discontinuations, 1 (11.1%) discontinued due to common early-onset TEAEs, which occurred at week 8; this participant reported both headache (n = 1; 0.6%) and nausea (n = 1; 0.6%) as the reasons for discontinuation. The remaining TEAE-related discontinuations among participants taking solriamfetol were due to other TEAEs, most of which were reported for 1 participant each, except for cataplexy (n = 2). Among placebo-treated participants with TEAE-related discontinuations, none were due to common early-onset TEAEs.

DISCUSSION

In general, the common early-onset TEAEs reported during week 1 were similar between participants with OSA and participants with narcolepsy, although rates were higher among participants with narcolepsy. To summarize, common early-onset TEAEs for participants with OSA included headache, nausea, decreased appetite, anxiety, insomnia, and feeling jittery, whereas common early-onset TEAEs for participants with narcolepsy included headache, nausea, decreased appetite, and dry mouth. The incidence of new or increased-severity early-onset TEAEs identified during week 1 decreased over time in both populations, with most events being mild to moderate in severity. At approved doses (≤ 150 mg), headache, nausea, and feeling jittery had median durations ≤ 8 days, whereas decreased appetite, anxiety, insomnia, and dry mouth had longer durations. Finally, 25 (7.0%) and 9 (5.1%) of participants receiving solriamfetol had TEAEs leading to study drug discontinuation compared with 4 (3.4%) and 1 (1.7%) receiving placebo for OSA and narcolepsy, respectively. Among those with TEAE-related discontinuations of solriamfetol, common early-onset TEAEs accounted for 44% and 11% of TEAE-related discontinuations in participants with OSA and narcolepsy, respectively.

These findings are important for a number of reasons. First, they suggest that AEs that occur with the highest frequency in the first week after starting solriamfetol treatment are unlikely to emerge later in the course of therapy. This pattern is instructive for clinical evaluation of response to treatment as it informs clinicians that patients are unlikely to develop AEs after the drug-initiation period. Second, serious AEs were uncommon (∼1% solriamfetol vs ∼1% placebo), and there were no observed deaths in either trial.

The choice to use solriamfetol needs to be made in the context of other available therapies. Several pharmacotherapies exist for the treatment of EDS in narcolepsy or OSA, including

Table 2—Common early-onset TEAEs during week 1.

	OSA							Narcolepsy					
		Solriamfetol							Solriamfetol				
	Placebo (n = 119)	37.5 mg (n = 58)	75 mg (n = 62)	150 mg (n = 117)	300 mg (n = 118)	Combined (All Doses) (n = 355)	Combined (Doses ≤ 150 mg) (n = 237)	Placebo (n = 59)	75 mg (n = 59)	150 mg (n = 59)	300 mg (n = 59)	Combined (All Doses) (n = 177)	Combined (Doses ≤ 150 mg) (n = 118)
Headache	6 (5.0)	3 (5.2)	3 (4.8)	6 (5.1)	6 (5.1)	18 (5.1)	12 (5.1)	1 (1.7)	2 (3.4)	8 (13.6)	11 (18.6)	21 (11.9)	10 (8.5)
Nausea	2 (1.7)	2 (3.5)	1 (1.6)	3 (2.6)	7 (5.9)	13 (3.7)	6 (2.5)	0	1 (1.7)	4 (6.8)	5 (8.5)	10 (5.7)	5 (4.2)
Decreased appetite	0	1 (1.7)	2 (3.2)	7 (6.0)	10 (8.5)	20 (5.6)	10 (4.2)	0	3 (5.1)	4 (6.8)	7 (11.9)	14 (7.9)	7 (5.9)
Anxiety	0	1 (1.7)	1 (1.6)	3 (2.6)	9 (7.6)	14 (3.9)	5 (2.1)	—	—	—	—	—	—
Insomnia	0	1 (1.7)	0	2 (1.7)	8 (6.8)	11 (3.1)	3 (1.3)	—	—	—	—	—	—
Feeling jittery	0	3 (5.2)	3 (4.8)	1 (0.9)	6 (5.1)	13 (3.7)	7 (3.0)	—	—	—	—	—	—
Dry mouth	—	—	—	—	—	—	—	2 (3.4)	1 (1.7)	4 (6.8)	4 (6.8)	9 (5.1)	5 (4.2)

Values are n (%). Cells with "—" indicate that the TEAE was not a common early-onset TEAE in the given study population. OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event.

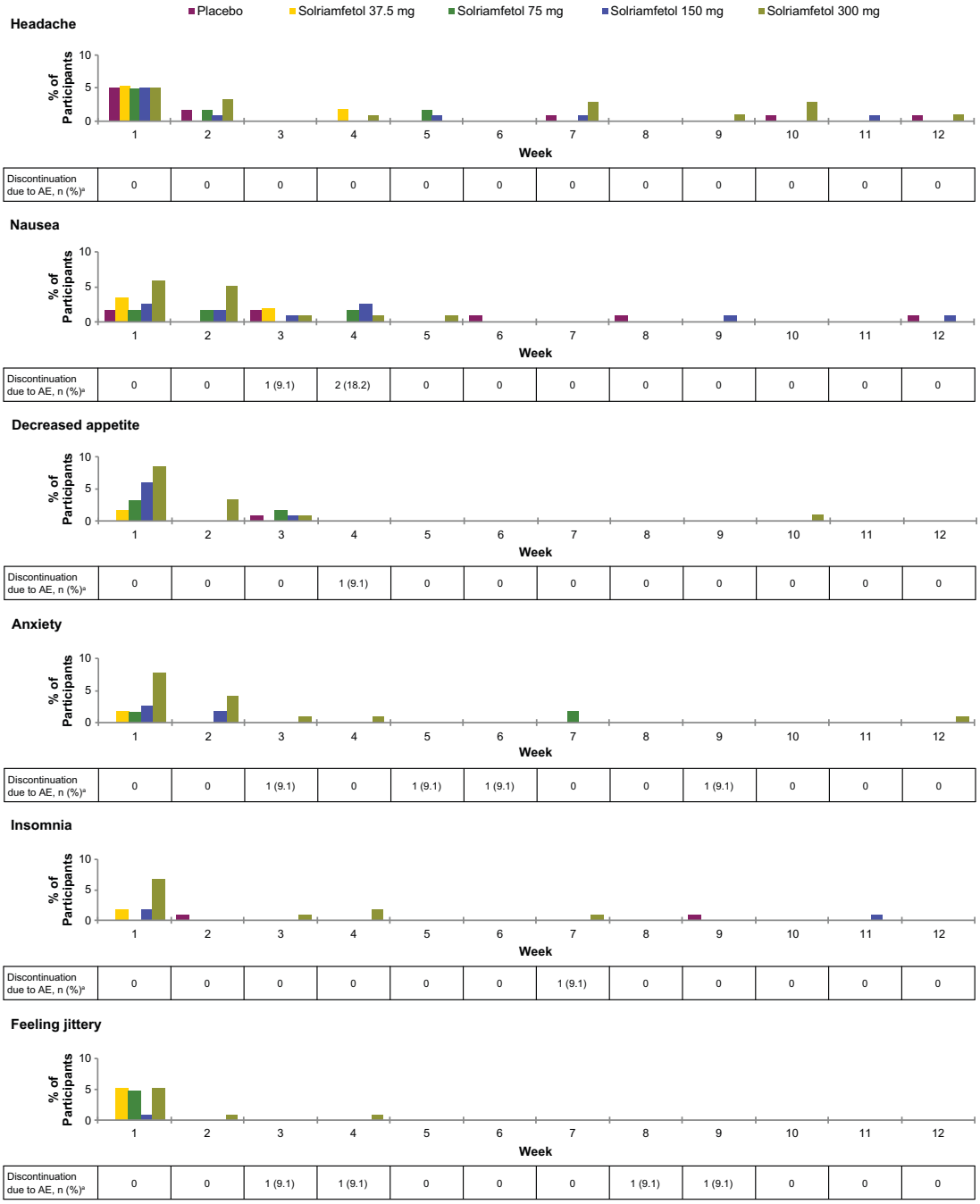
stimulants, wake-promoting agents, and sodium oxybate (narcolepsy only).[10–14,16,29–31] The most common side effects associated with sodium oxybate (Xyrem; Jazz Pharmaceuticals, Palo Alto, CA) in patients with narcolepsy are nausea, dizziness, vomiting, somnolence, enuresis, and tremor.[14] In the case of stimulants, such as methylphenidate (Ritalin; Novartis Pharmaceuticals Corporation, East Hanover, NJ),[13] amphetamine salts (Adderall; Teva Pharmaceuticals, Horsham, PA),[29] or dextroamphetamine (Dexedrine; Teva Pharmaceuticals, North Wales, PA),[30] minimal efficacy or safety data are available in patients with OSA or narcolepsy as, to our knowledge, there have been no randomized controlled trials conducted in these patient populations. Generally, stimulants have high abuse potential and are associated with more AEs than other available therapies.[13,29,30] The side effect most commonly associated with the wake-promoting agents modafinil and armodafinil is headache.[32] Pitolisant is another wake-promoting agent approved for treatment of EDS and cataplexy in patients with narcolepsy (Wakix; Harmony Biosciences, Plymouth Meeting, PA)[12,33] and recently was approved in the EU to improve wakefulness and reduce EDS in adults with OSA whose EDS has not been treated satisfactorily by a primary treatment for OSA or who do not tolerate CPAP (Ozawade; Bioprojet, Paris, France).[34–36] AEs of pitolisant are similar to those associated with other wake-promoting agents, with headache, insomnia, and nausea being the most common.[34]

It is important to note that solriamfetol has previously been shown to increase blood pressure and heart rate.[24,26] In the phase 3 trial of solriamfetol in OSA, solriamfetol was associated with mean changes in systolic blood pressure (0.5 to 2.5 mmHg), diastolic blood pressure (–0.2 to 1.5 mmHg), and heart rate (0.7–2.9 beats/minute) for 9 hours postdose, with the highest increases associated with the 300-mg dose.[24] After 12 weeks of solriamfetol treatment, these increases were not present when blood pressure was measured prior to dosing, suggesting they are transient and correspond with expected peak plasma concentrations of solriamfetol. Similarly, in the phase 3 trial of solriamfetol in narcolepsy, participants treated with solriamfetol showed mean increases in systolic blood pressure (0.3 to 2.0 mmHg), diastolic blood pressure (1.0 to 2.1 mmHg), and heart rate (0.6 to 4.3 beats/minute); no participant had a TEAE of hypertension but 2 had a TEAE of increased blood pressure.[26] Hypertension should therefore be controlled prior to initiating and monitored periodically throughout treatment.[22] In addition, solriamfetol is contraindicated with monoamine oxidase inhibitors.[22]

While these agents improve patients' symptoms, they do not address underlying disease. Primary therapy for OSA is often needed in conjunction with symptomatic treatment of EDS for optimal response. In the case of OSA, treatment of the underlying disease with CPAP or an oral appliance is recommended, as are efforts to optimize adherence.

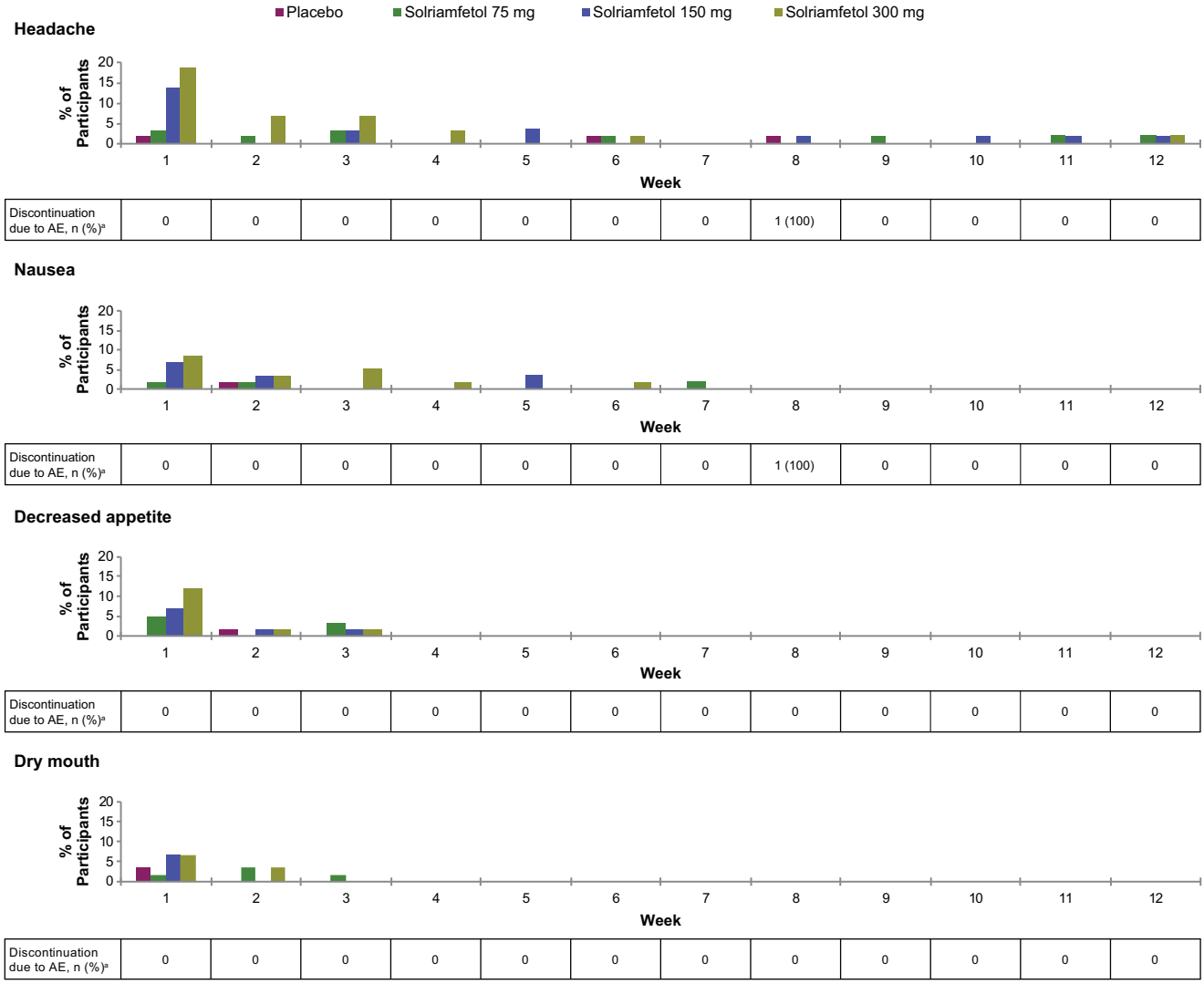
The current analysis had several strengths, including a reasonable sample size, clinically important outcomes, and rigorous AE reporting in the context of a clinical trial. However, there were also a number of limitations. First, these were post hoc analyses of prospectively collected data and were not

Figure 1—Incidence of new or increased-severity TEAEs for the most common early-onset TEAEs in participants in the OSA study.



All events depicted represent new-onset TEAEs with the exception of 1 event reported by a participant in the OSA study who had worsening of an existing TEAE of headache, which increased in severity from 1 (mild) at the beginning of the study to 2 (moderate) at the end of the study. Participants could list > 1 TEAE as reason for discontinuation (hence, the sum of those discontinuing due to individual TEAEs is greater than the overall discontinuations due to TEAEs). [a]Percentage of participants who discontinued due to AEs is based on the total number of participants who discontinued due to any common early-onset TEAE (n = 11). AE = adverse event, OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event.

Figure 2—Incidence of new or increased-severity TEAEs for the most common early-onset TEAEs in participants in the narcolepsy study.



All events depicted represent new-onset TEAEs. Participants could list > 1 TEAE as reason for discontinuation (hence, the sum of those discontinuing due to individual TEAEs is greater than the overall discontinuations due to TEAEs). [a]Percentage of participants who discontinued due to AEs is based on the total number of participants who discontinued due to any common early-onset TEAE (n = 1). AE = adverse event, TEAE = treatment-emergent adverse event.

powered to detect rare AEs. Second, these studies were limited to 12 weeks in duration and the evolution of AEs over a longer-term treatment cannot be characterized based on these studies. However, these data suggest that the majority of AEs and serious AEs occur early and do not suggest that late AEs emerge over time. This is consistent with data from a long-term open-label extension study, which showed that the majority of common TEAEs occurred during the first 2 weeks of the study.[27] Third, because these studies were controlled trials that included specific inclusion and exclusion criteria, they may not be representative of real-world data. In addition, participants were randomly assigned to dose groups, rather than titrated to an efficacious and tolerable dose as would likely be done in clinical practice (ie, participants randomized to receive 150 or 300 mg underwent a 3-day titration prior to receiving their assigned dose). As such, the AE profile observed in the current studies is representative of treatment with these stable doses following initial titration. Treatment with doses higher than 150 mg should be avoided in accordance with the prescribing recommendations and due to increased potential for TEAEs. Finally, no head-to-head comparisons of solriamfetol with other medications (eg, modafinil, sodium oxybate, methylphenidate, or pitolisant) have been conducted to our knowledge. As such, conclusions regarding comparative effectiveness are indirect. Despite these limitations, these findings provide evidence that may inform clinical direction until more definitive data emerge in the future.

In conclusion, the study's findings can enhance clinician understanding of the evolution of TEAEs during solriamfetol treatment, which would help them to better inform their

Table 3—Duration of common early-onset TEAEs.

	OSA						Narcolepsy					
	Placebo (n = 119)		Combined Solriamfetol (All Doses) (n = 355)		Combined Solriamfetol (Doses ≤ 150 mg) (n = 237)		Placebo (n = 59)		Combined Solriamfetol (All Doses) (n = 177)		Combined Solriamfetol (Doses ≤ 150 mg) (n = 118)	
TEAE	Events, n	Median Duration (Min, Max), Days	Events, n	Median Duration (Min, Max), Days	Events, n	Median Duration (Min, Max), Days	Events, n	Median Duration (Min, Max), Days	Events, n	Median Duration (Min, Max), Days	Events, n	Median Duration (Min, Max), Days
Headache	13	1 (1, 86)	40	5.5 (1, 112)	20	8 (1, 86)	3	2 (1, 84)	53	2 (1, 122)	27	2 (1, 122)
Nausea	7	3 (1, 83)	33	10 (1, 86)	17	8 (1, 86)	1	4 (4, 4)	25	5 (1, 77)	11	5 (1, 77)
Decreased appetite	1	68 (68, 68)	28	57 (5, 91)	13	18 (6, 83)	1	16 (16, 16)	20	79 (1, 120)	11	80 (1, 96)
Anxiety	0	n/a	25	26 (1, 94)	9	36 (1, 94)	—	—	—	—	—	—
Insomnia	2	6 (2, 10)	16	8.5 (1, 49)	4	21 (1, 49)	—	—	—	—	—	—
Feeling jittery	0	n/a	15	4 (1, 49)	7	4 (3, 49)	—	—	—	—	—	—
Dry mouth	—	—	—	—	—	—	2	1.5 (1, 2)	13	80 (1, 104)	7	82 (8, 104)

Safety population. Cells with "—" indicate that the TEAE was not a common early-onset TEAE in the given study population. n/a = not available, Max = maximum, Min = minimum, OSA = obstructive sleep apnea, TEAE = treatment-emergent adverse event.

patients. Specifically, prescribing physicians can advise patients that common early-onset AEs with solriamfetol are typically limited in duration. Although some AEs appear to persist for over 2 months (eg, decreased appetite), the majority subside during the first week of treatment (eg, headache and nausea). Further research on the benefit/risk profiles of available pharmacotherapies will help optimize the care of individuals with OSA and those with narcolepsy.

ABBREVIATIONS

CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
OSA, obstructive sleep apnea
TEAE, treatment-emergent adverse event
TONES, Treatment of OSA and Narcolepsy Excessive Sleepiness

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Address correspondence to: Russell Rosenberg, PhD, Chief Science Officer and CEO, NeuroTrials Research, Inc, 5887 Glenridge Drive, STE 400, Atlanta, GA 30328; Tel: (404) 851-9934; Email: rrosenberg@neurotrials.com

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