# Solriamfetol for the treatment of excessive daytime sleepiness in participants with narcolepsy with and without cataplexy: subgroup analysis of efficacy and safety data by cataplexy status in a randomized controlled trial

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ORIGINAL RESEARCH ARTICLE

# Solriamfetol for the Treatment of Excessive Daytime Sleepiness in Participants with Narcolepsy with and without Cataplexy: Subgroup Analysis of Efficacy and Safety Data by Cataplexy Status in a Randomized Controlled Trial

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## Abstract

**Background** Solriamfetol, a dopamine/norepinephrine reuptake inhibitor, improved wakefulness and reduced excessive daytime sleepiness (EDS) in studies of participants with narcolepsy with and without cataplexy.

**Objective** Prespecified subgroup analyses of data from a 12-week randomized, double-blind, placebo-controlled, phase III trial of solriamfetol for EDS in narcolepsy evaluated the efficacy and safety of solriamfetol by cataplexy status.

**Methods** Participants with narcolepsy received solriamfetol (75, 150, or 300 mg/day) or placebo and were stratified by cataplexy status. Coprimary endpoints were change from baseline on Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS); Patient Global Impression of Change (PGI-C) was the key secondary endpoint. Change in frequency of cataplexy attacks was evaluated in participants reporting cataplexy at baseline. Safety was evaluated. No adjustments were made for multiple comparisons; therefore *p* values are nominal.

**Results** There were 117 participants in the cataplexy subgroup and 114 in the non-cataplexy subgroup. At week 12, least-squares (LS) mean (95% confidence interval [CI]) differences from placebo on change from baseline in MWT for solriamfetol 75, 150, and 300 mg in the cataplexy subgroup were 1.6 (− 3.6 to 6.9), 6.1 (0.7–11.4), and 8.9 (3.5–14.2) minutes, respectively ($p < 0.05$; 150 and 300 mg), and in the non-cataplexy subgroup were 3.4 (− 1.9 to 8.7), 9.1 (3.8–14.3), and 11.2 (5.8–16.6) minutes, respectively ($p < 0.001$; 150 and 300 mg). At week 12, LS mean (95% CI) differences from placebo on ESS change from baseline for solriamfetol 75, 150, and 300 mg in the cataplexy subgroup were − 1.3 (− 3.9 to 1.3), − 3.7 (− 6.4 to − 1.1), and − 4.5 (− 7.1 to − 1.9), respectively ($p < 0.01$; 150 and 300 mg), and in the non-cataplexy subgroup were − 3.0 (− 5.6 to − 0.4), − 3.7 (− 6.3 to − 1.2), and − 4.9 (− 7.6 to − 2.2), respectively ($p < 0.05$; all doses). For PGI-C at week 12, the mean percentage difference from placebo (95% CI) for solriamfetol 75, 150, and 300 mg in the cataplexy subgroup was 10% (− 15 to 35), 33% (9–57), and 39% (16–61), respectively ($p < 0.05$; 150 and 300 mg), and in the non-cataplexy subgroup was 48% (25–70), 44% (21–67), and 52% (30–73), respectively ($p < 0.001$; all doses), with somewhat differential treatment effects for 75 mg by cataplexy status. No changes in the number of cataplexy attacks were observed for solriamfetol compared with placebo (mean ± standard deviation changes: − 3.6 ± 13.3 [combined solriamfetol] and − 3.5 ± 9.8 [placebo]). Common adverse events (headache, nausea, decreased appetite, and nasopharyngitis) were similar between cataplexy subgroups.

**Conclusions** These data strongly indicate that solriamfetol was effective in treating EDS in participants with narcolepsy with or without cataplexy, as indicated by robust effects on MWT, ESS, and PGI-C. The safety profile was similar regardless of cataplexy status.

**Trial Registration and Date** ClinicalTrials.gov NCT02348593. 28 January 2015.

Lawrence Lee is a former employee of Jazz Pharmaceuticals.

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**Key Points**

These data from a 12-week, randomized, placebo-controlled, multicenter, parallel-group clinical trial demonstrate that solriamfetol was effective in treating excessive daytime sleepiness in participants with narcolepsy and with and without cataplexy.

Effects on the Maintenance of Wakefulness Test, Epworth Sleepiness Scale, and Patient Global Impression of Change appeared to be robust regardless of cataplexy status.

The safety profile of solriamfetol was similar in participants with and without cataplexy, with no new safety findings.

## 1 Introduction

Narcolepsy is a neurologic disease for which there is no known cure [1]. The five core symptoms of narcolepsy are excessive daytime sleepiness (EDS), cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep [1–4]. Cataplexy has been estimated to occur in approximately 60–90% of patients with narcolepsy [5–7].

There are two subtypes of narcolepsy: type 1 (previously named narcolepsy with cataplexy) and type 2 (previously named narcolepsy without cataplexy) [8]. Both are characterized by severe EDS, with short sleep latency and sleep-onset rapid eye movement periods on the mean sleep latency test. However, they differ in pathophysiology: type 1 is characterized by orexin/hypocretin-1 deficiency with low cerebrospinal fluid (CSF) hypocretin-1 levels, whereas type 2 is characterized by normal or marginally decreased CSF hypocretin-1 levels [8]. Few studies have examined the response to treatments for narcolepsy based on the presence or absence of cataplexy [9].

Solriamfetol, a dopamine and norepinephrine reuptake inhibitor [10], has been approved in the USA and EU for EDS associated with narcolepsy or obstructive sleep apnea (OSA) [11, 12]. The approved dose range for narcolepsy is 75–150 mg once daily [11, 12]. Solriamfetol demonstrated robust wake-promoting effects in two randomized controlled 12-week studies [13, 14] that enrolled participants with both narcolepsy subtypes. The objective of this current analysis was to further evaluate the efficacy and safety of solriamfetol in subgroups of participants with or without cataplexy from the largest of the randomized controlled trials of solriamfetol in narcolepsy [14].

## 2 Methods

### 2.1 Study Design

The methods of this study have been previously reported [14] and are summarized here. This 12-week, randomized, double-blind, placebo-controlled study (ClinicalTrials.gov registry: NCT02348593) was conducted at 59 study centers (50 in the USA and Canada; nine in Finland, France, Germany, and Italy) from 19 May 2015 (first participant enrollment) until 14 February 2017 (last participant visit). The study was approved by institutional review boards or ethics committees at all sites and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Participants were randomized 1:1:1:1—stratified based on presence or absence of cataplexy—to receive once-daily doses of solriamfetol 75, 150, or 300 mg or placebo. Participants randomized to solriamfetol 150 or 300 mg received 75 or 150 mg, respectively, on days 1 through 3 and then received the 150- or 300-mg dose starting on day 4. Participants randomized to the 75-mg dose received the 75-mg dose from day 1. Study drugs were prepared in identical opaque gelatin capsules to ensure adequate blinding, and study personnel and participants were blinded to study treatments. Treatment assignments were provided to the investigator via an interactive voice or web response system.

### 2.2 Participants

All participants met diagnostic criteria for narcolepsy according to the *International Classification of Sleep Disorders*, *Third Edition* [8] or *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* [15]. Participants with and without cataplexy were eligible.

Participants were eligible if they were aged 18–75 years, had a baseline mean sleep latency < 25 min on the first four trials of a five-trial, 40-min Maintenance of Wakefulness Test [MWT]) [16], baseline Epworth Sleepiness Scale (ESS) [17] score ≥ 10 despite usual nightly sleep ≥ 6 h, and body mass index (BMI) of 18 to < 45 kg/m$^2$. Participants consented to use a medically acceptable method of contraception during and 30 days before and after study participation.

Participants were excluded if they had medical conditions/behaviors other than narcolepsy (e.g., shift-work disorder) or took medications (e.g., over-the-counter sleep aids or stimulants, hypnotics, benzodiazepines, barbiturates, opioids, sodium oxybate, or anticataplectics such as antidepressants or anticonvulsants) that could affect the evaluation of EDS or cataplexy, or could affect the safety of the participant. Participants were required to discontinue all prohibited medications prior to randomization, with a washout

period corresponding to at least five half-lives of the drug and a return to baseline symptoms for at least 7 days prior to baseline assessment.

### 2.3 Assessments and Endpoints

Participants attended clinic visits at baseline and weeks 1, 4, 8, and 12 (or early termination) and a safety follow-up visit at week 14. Baseline assessments included ESS and MWT. The ESS is a patient-rated scale that assesses an individual's average sleep propensity in daily life. It includes eight items scored from 0 to 3, with higher scores indicating greater sleepiness; scores > 10 are generally considered indicative of EDS [17]. The MWT is a polysomnographic procedure that provides an objective measure of an individual's ability to remain awake during the daytime in a darkened, quiet environment; generally, a mean sleep latency < 19 min is considered indicative of impaired wakefulness [16].

Post-baseline assessments included ESS and Patient and Clinician Global Impression of Change (PGI-C and CGI-C, respectively) at weeks 1, 4, 8, and 12 and MWT at weeks 1, 4, and 12. Participants with cataplexy used daily cataplexy frequency diaries to record the occurrence and number of cataplexy attacks they had each day; cataplexy diaries were reviewed at each visit.

The coprimary endpoints were change from baseline to week 12 in MWT sleep latency and ESS score. The key secondary endpoint was percentage of participants who reported improvement (defined as "minimally improved," "much improved," or "very much improved") on the PGI-C at week 12. Change in weekly number of cataplexy attacks was an exploratory endpoint in the cataplexy subgroup. Safety assessments included treatment-emergent adverse events (TEAEs), which were assessed throughout the study.

### 2.4 Analysis

Demographics and baseline clinical characteristics are summarized by treatment group and cataplexy status. Post hoc analyses were conducted to evaluate differences in baseline values for MWT mean sleep latency and ESS scores in subgroups of participants by cataplexy status (i.e., participants with or without cataplexy) using two-sample *t* tests.

Efficacy was evaluated using the modified intent-to-treat (mITT) population (participants who received at least one study drug dose and had baseline and at least one post-baseline MWT or ESS value). Prespecified subgroup analyses were conducted on key efficacy and safety endpoints by cataplexy status. Analyses of MWT and ESS endpoints in the subgroups with and without cataplexy used a mixed-effect repeated-measures model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value. A Chi-squared test was used for analysis of the percentage of participants improved on PGI-C and CGI-C. Exploratory post hoc analyses were performed to investigate potential differences in solriamfetol treatment effects between participants with and without cataplexy. To test for effect modification by cataplexy status, an interaction term (treatment × visit × cataplexy status) was included in the model used for the primary analysis of MWT and ESS; a Breslow–Day–Tarone test was used to test homogeneity of the odds ratio for improvement (improved/not improved) at week 12 on PGI-C by cataplexy status.

A Wilcoxon rank-sum test was used for comparisons between solriamfetol and placebo in change from baseline in weekly cataplexy attacks in the cataplexy subgroup.

This study was not powered for analyses of exploratory endpoints or subgroups. No adjustments were made for multiplicity of testing within the subgroups; therefore, all *p* values presented are nominal.

## 3 Results

### 3.1 Participant Disposition and Demographics

Participant disposition is illustrated in Fig. 1. Baseline age, sex, race, and BMI were similar between participants with and without cataplexy (Table 1). Approximately 50% of the study population had cataplexy, and most participants were rated as being markedly ill or worse at baseline. Baseline mean (95% confidence interval [CI]) sleep latencies on MWT were 6.6 min (5.5–7.7) in participants with cataplexy and 8.5 min (7.5–9.6) in those without cataplexy ($p = 0.0108$ for participants with vs. without cataplexy); mean (95% CI) ESS scores at baseline were 17.8 (17.3–18.4) and 16.5 (15.9–17.1), respectively ($p = 0.0012$ for participants with vs. without cataplexy).

### 3.2 Efficacy Results

Changes in sleep latency (minutes) on MWT and in ESS score from baseline to week 12 were generally similar in participants with or without cataplexy, with effects observed in both subgroups at the 150- and 300-mg doses as early as week 1.

In the cataplexy subgroup, least-squares (LS) mean changes (95% CI) from baseline to week 12 in MWT sleep latency were 3.4 (− 0.4 to 7.2), 7.9 (4.1–11.7), and 10.7 (6.8–14.5) for solriamfetol 75, 150, and 300 mg, respectively, compared with 1.8 (− 1.9 to 5.4) for placebo ($p < 0.05$ for 150 and 300 mg; Fig. 2). In the non-cataplexy subgroup, LS mean (95% CI) changes from baseline to week 12 in MWT sleep latency were 6.0 (2.2–9.8), 11.6 (7.9–15.4), and 13.8 (9.8–17.8) for solriamfetol 75, 150, and 300 mg,

respectively, compared with 2.6 (− 1.1 to 6.2) for placebo ($p < 0.05$ and 0.0001 for 150 and 300 mg, respectively; Fig. 2).

At week 12, LS mean changes from baseline for individual MWT trials reflected increases in sleep latency across the day with solriamfetol 150 mg and 300 mg in participants with cataplexy and without cataplexy (Fig. 3).

In the cataplexy subgroup, LS mean (95% CI) changes from baseline to week 12 in ESS scores were − 3.1 (− 5.0 to − 1.2), − 5.6 (− 7.5 to − 3.7), and − 6.3 (− 8.2 to − 4.5) for solriamfetol 75, 150, and 300 mg, respectively, compared with − 1.8 (− 3.7 to − 0.02) for placebo ($p < 0.05$ for 150 and 300 mg; Fig. 4). In the subgroup without cataplexy, LS mean (95% CI) changes from baseline to week 12 in ESS scores were − 4.5 (− 6.4 to − 2.6), − 5.2 (− 7.1 to − 3.4), and − 6.4 (− 8.4 to − 4.4) for solriamfetol 75, 150, and 300 mg, respectively, compared with − 1.5 (− 3.3 to 0.3) for placebo ($p < 0.05$ for all solriamfetol doses; Fig. 4).

From week 1 to week 12, most participants reported improvement on the PGI-C in both subgroups (Fig. 5). At each solriamfetol dose, a numerically higher percentage of participants without cataplexy reported improvement on the PGI-C compared with participants with cataplexy, and this difference was most notable at the lowest dose of solriamfetol (75 mg). Improvement on the CGI-C followed a generally similar pattern (Electronic Supplementary Material [ESM] 1).

In the exploratory post hoc analyses of potential modification of solriamfetol treatment effects by cataplexy status, minimal or no evidence of heterogeneity was observed (Fig. 6). Specifically, there was no treatment-by-visit-by-cataplexy interaction for any of the dose groups on the MWT or ESS (all interactions $p > 0.05$; Fig. 6a, b). For the PGI-C (Fig. 6c), greater effects were observed for participants without cataplexy compared with those with cataplexy in the 75-mg dose group only (interaction $p = 0.03$).

Among the participants with cataplexy, the mean and median number of weekly cataplexy attacks in all treatment groups remained relatively constant throughout the study. No consistent pattern was observed in the number of cataplexy attacks as the study progressed (data not shown). Change from baseline in the mean weekly numbers of cataplexy attacks during weeks 9–12 generally showed numerically larger reductions in participants with more frequent cataplexy attacks in both the solriamfetol and the placebo group, except in participants in the 300-mg dose group (Table 2). Specifically, the 75- and 150-mg doses were associated with a greater reduction in cataplexy attacks compared with placebo among participants with a baseline frequency of more than ten cataplexy attacks per week. There were no structured assessments of effects on other symptoms of narcolepsy—namely, hypnagogic and hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep.

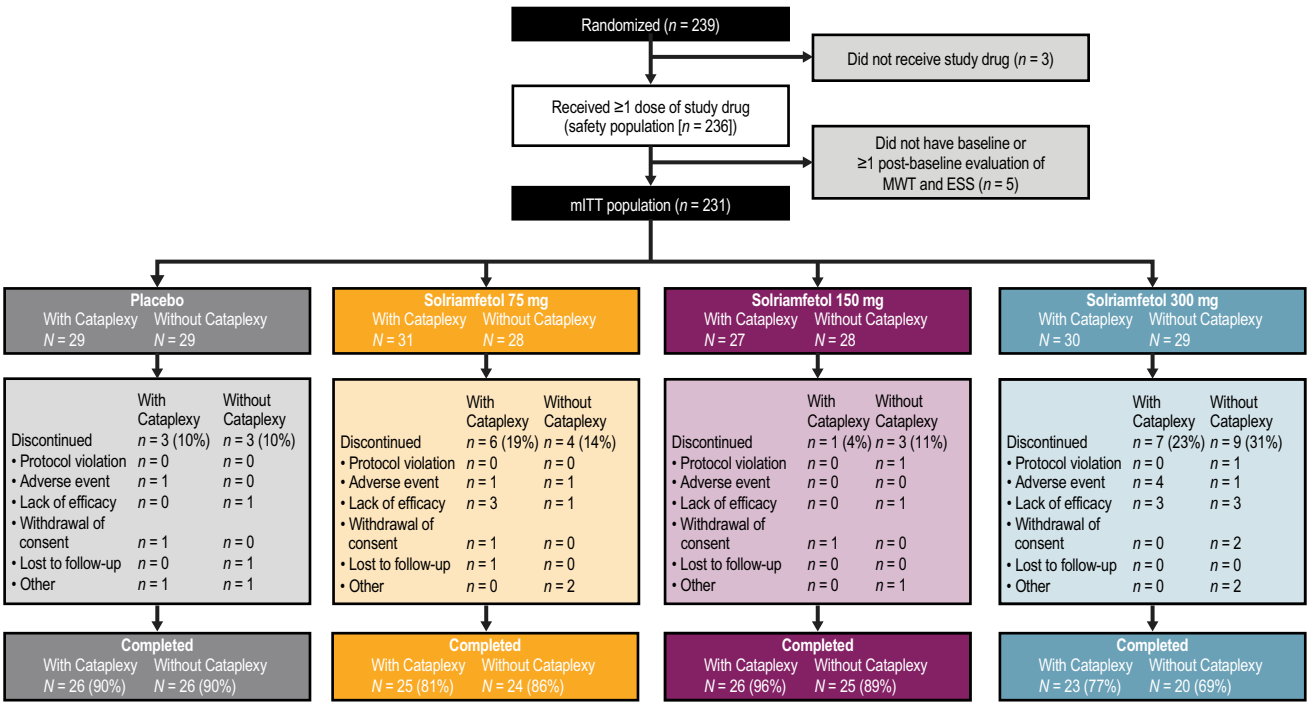



**Fig. 1** Participant disposition flow diagram. *ESS* Epworth Sleepiness Scale, *mITT* modified intent-to-treat, *MWT* Maintenance of Wakefulness Test

**Table 1** Baseline demographics (mITT population)

| Demographics | With cataplexy | | | Without cataplexy | | |
|---|---|---|---|---|---|---|
| | Placebo ($n=29$) | Solriamfetol ($n=88$) | Total ($n=117$) | Placebo ($n=29$) | Solriamfetol ($n=85$) | Total ($n=114$) |
| Age, years | 39.3 ± 17.0 | 36.8 ± 12.0 | 37.4 ± 13.3 | 33.1 ± 12.7 | 35.6 ± 13.0 | 35.0 ± 12.9 |
| Female | 19 (65.5) | 58 (65.9) | 77 (65.8) | 15 (51.7) | 58 (68.2) | 73 (64.0) |
| Race | | | | | | |
| Asian | 0 (0) | 3 (3.4) | 3 (2.6) | 0 (0) | 3 (3.5) | 3 (2.6) |
| Black/African American | 4 (13.8) | 8 (9.1) | 12 (10.3) | 6 (20.7) | 15 (17.6) | 21 (18.4) |
| White | 25 (86.2) | 75 (85.2) | 100 (85.5) | 21 (72.4) | 63 (74.1) | 84 (73.7) |
| Other | 0 (0) | 2 (2.3) | 2 (1.7) | 2 (6.9) | 4 (4.8) | 6 (5.3) |
| BMI, kg/m$^2$ | 29.2 ± 6.2 | 28.3 ± 6.1 | 28.5 ± 6.1 | 29.4 ± 5.5 | 27.6 ± 5.5 | 28.1 ± 5.5 |
| MWT sleep latency, min | 4.4 ± 5.1 (2.4–6.3) | 7.3 ± 5.8 (6.1–8.6) | 6.6 ± 5.8[a] (5.5–7.7) | 7.9 ± 5.8 (5.7–10.1) | 8.8 ± 5.6 (7.5–10.0) | 8.5 ± 5.7[a] (7.5–9.6) |
| ESS score | 18.2 ± 3.0 (17.0–19.3) | 17.7 ± 3.3 (17.0–18.4) | 17.8 ± 3.2[b] (17.3–18.4) | 16.3 ± 2.4 (15.4–17.3) | 16.6 ± 3.2 (15.9–17.2) | 16.5 ± 3.0[b] (15.9–17.1) |
| Weekly cataplexy attacks ($n$) | 13.0 ± 14.9 (28) | 13.5 ± 20.0 (87) | 13.4 ± 18.9 (115) | – | – | – |
| Baseline CGI-S | | | | | | |
| 1 = Normal, not at all ill | – | – | – | – | – | – |
| 2 = Borderline ill | – | – | – | – | – | – |
| 3 = Mildly ill | 1 (3.4) | 2 (2.3) | 3 (2.6) | 0 (0) | 5 (5.9) | 5 (4.4) |
| 4 = Moderately ill | 4 (13.8) | 18 (20.5) | 22 (18.8) | 10 (34.5) | 28 (32.9) | 38 (33.3) |
| 5 = Markedly ill | 11 (37.9) | 31 (35.2) | 42 (35.9) | 14 (48.3) | 33 (38.8) | 47 (41.2) |
| 6 = Severely ill | 10 (34.5) | 28 (31.8) | 38 (32.5) | 3 (10.3) | 13 (15.3) | 16 (14.0) |
| 7 = Among the most extremely ill | 3 (10.3) | 9 (10.2) | 12 (10.3) | 1 (3.4) | 6 (7.1) | 7 (6.1) |
| Missing | – | – | – | 1 (3.4) | 0 (0) | 1 (0.9) |

Data are presented as mean ± standard deviation (95% confidence interval) or $n$ (%) unless otherwise indicated

*BMI* body mass index, *CGI-S* Clinical Global Impression of Severity, *ESS* Epworth Sleepiness Scale, *mITT* modified intent to treat, *MWT* Maintenance of Wakefulness Test

[a]Comparison of baseline MWT values for cataplexy and without cataplexy subgroups: $p=0.0108$

[b]Comparison of baseline ESS scores for cataplexy and without subgroups: $p=0.0012$

### 3.3 Safety Results

The incidence of serious TEAEs, TEAEs leading to discontinuation, and the most common TEAEs (≥ 5%) were similar between participants with and without cataplexy and similar to those seen in the overall safety population (Table 3). Two serious TEAEs, non-cardiac chest pain and anxiety, were reported for one participant (in the without cataplexy subgroup); the TEAEs were considered by the investigator to be not related to study treatment, and the participant continued the study without recurrence of these AEs [14]. Ten participants (seven with cataplexy; three without cataplexy) experienced at least one TEAE leading to discontinuation (Table 3), including cataplexy, which was reported by two participants receiving solriamfetol and one participant receiving placebo (all reported a history of cataplexy at screening); no other TEAEs leading to discontinuation occurred in more than one participant. In both subgroups, headache, nasopharyngitis, decreased appetite, and nausea were among the most common TEAEs, in addition to dry mouth in participants with cataplexy, and anxiety and diarrhea in participants without cataplexy.

## 4 Discussion

In these prespecified subgroup analyses of a randomized controlled narcolepsy trial [14], the efficacy and safety of solriamfetol were evaluated based on the presence or absence of cataplexy. Solriamfetol was effective in treating

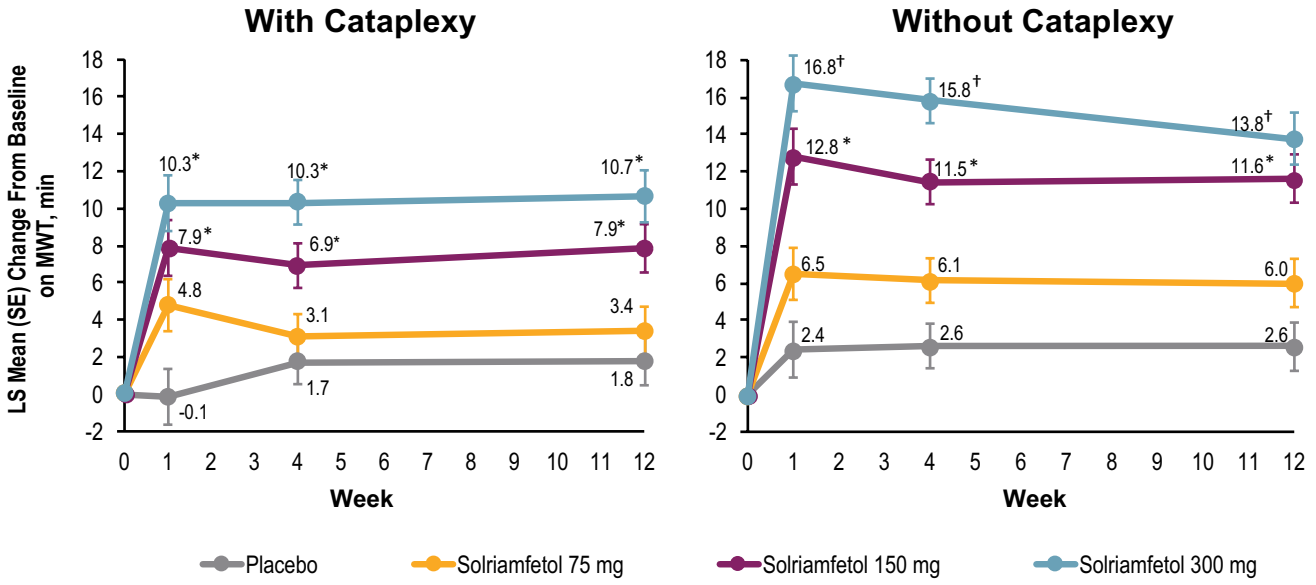



**Fig. 2** Change in sleep latency on MWT from baseline to week 12 in participants with and without cataplexy (mITT population). *$p<0.05$ and †$p<0.0001$ vs. placebo. Subgroup analyses were not powered for statistical significance and not controlled for multiplicity. With cataplexy: placebo ($n=29$), solriamfetol 75 mg ($n=31$), solriamfetol 150 mg ($n=27$), solriamfetol 300 mg ($n=30$). Without cataplexy: placebo ($n=29$), solriamfetol 75 mg ($n=28$), solriamfetol 150 mg ($n=28$), solriamfetol 300 mg ($n=29$). *LS* least squares, *mITT* modified intent to treat, *MWT* Maintenance of Wakefulness Test, *SE* standard error

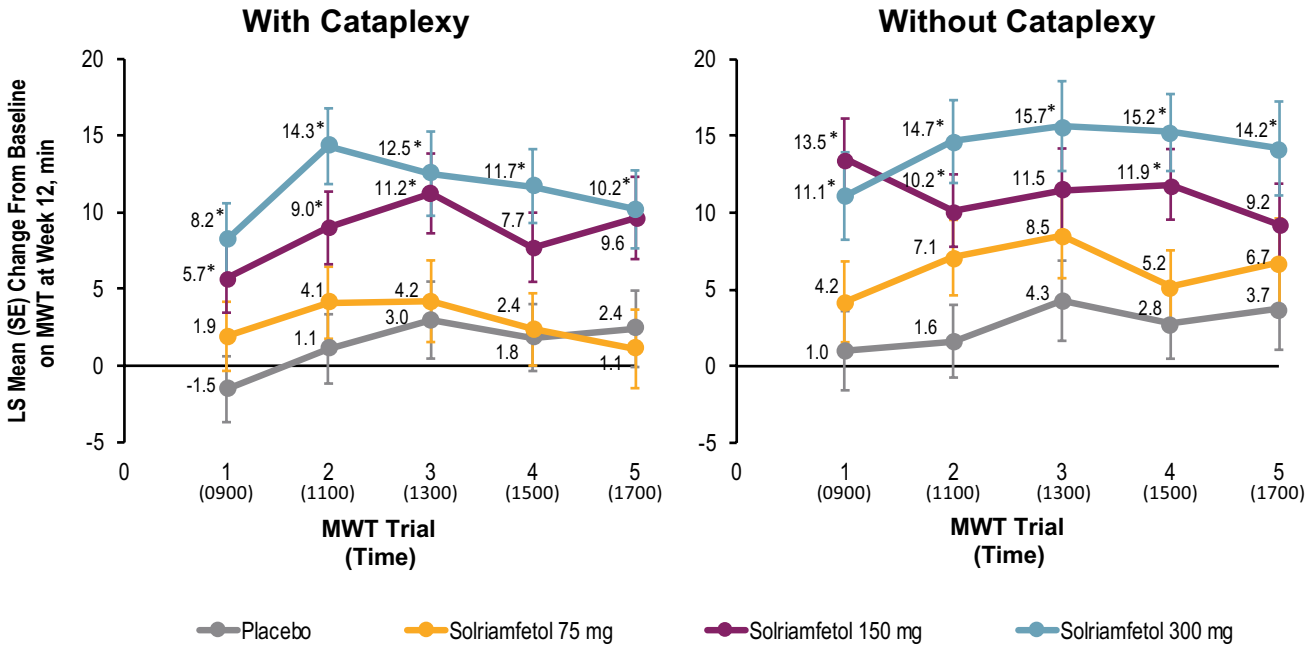



**Fig. 3** Change from baseline in sleep latency on each of five MWT trials at week 12 in participants with and without cataplexy (mITT population). *$p<0.05$ and †$p<0.0001$ vs. placebo. Subgroup analyses were not powered for statistical significance and not controlled for multiplicity. With cataplexy: placebo ($n=29$), solriamfetol 75 mg ($n=31$), solriamfetol 150 mg ($n=27$), solriamfetol 300 mg ($n=30$). Without cataplexy: placebo ($n=29$), solriamfetol 75 mg ($n=28$), solriamfetol 150 mg ($n=28$), solriamfetol 300 mg ($n=29$). *LS* least squares, *mITT* modified intent-to-treat, *MWT* Maintenance of Wakefulness Test, *SE* standard error

EDS in participants with or without cataplexy, as demonstrated by robust effects on the MWT, ESS, and PGI-C. The most robust effects were observed at 150 and 300 mg. The 75-mg dose did not appear to be as effective as higher doses in these subgroup analyses [11, 12]; however, the efficacy of this dose was demonstrated in the study's primary efficacy

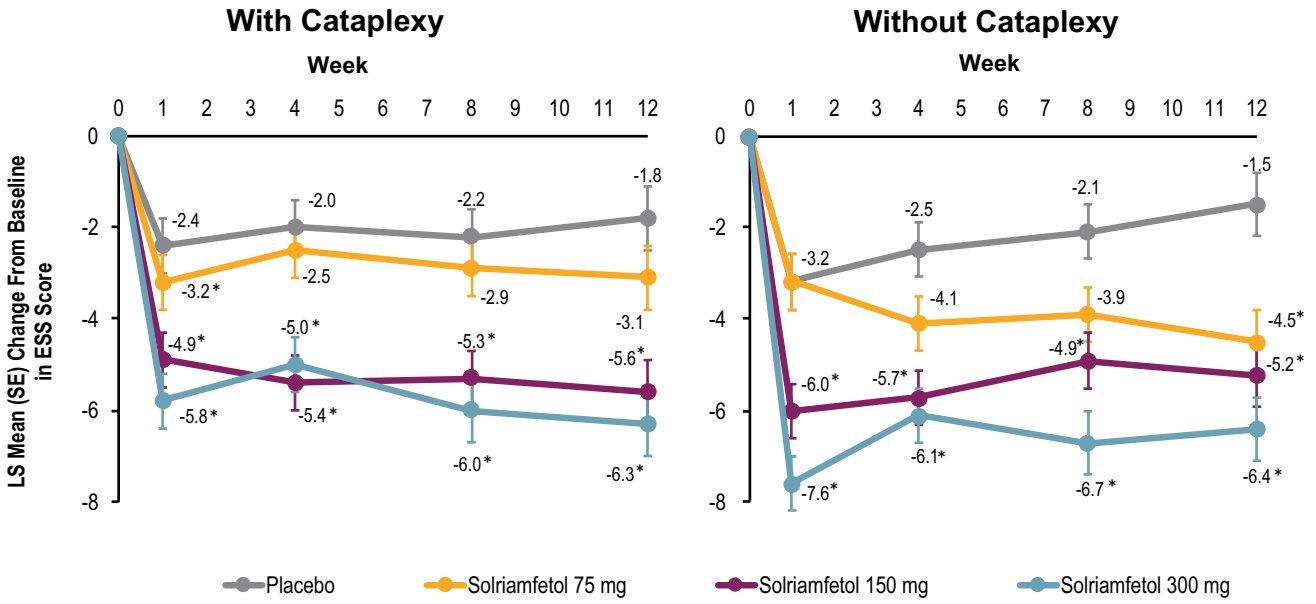



**Fig. 4** Change in ESS scores from baseline to week 12 in participants with and without cataplexy. *$p < 0.05$ vs. placebo. Subgroup analyses were not powered for statistical significance and not controlled for multiplicity. With cataplexy: placebo ($n = 29$), solriamfetol 75 mg ($n = 31$), solriamfetol 150 mg ($n = 27$), solriamfetol 300 mg ($n = 30$). Without cataplexy: placebo ($n = 29$), solriamfetol 75 mg ($n = 28$), solriamfetol 150 mg ($n = 28$), solriamfetol 300 mg ($n = 29$). *ESS* Epworth Sleepiness Scale, *LS* least squares, *SE* standard error

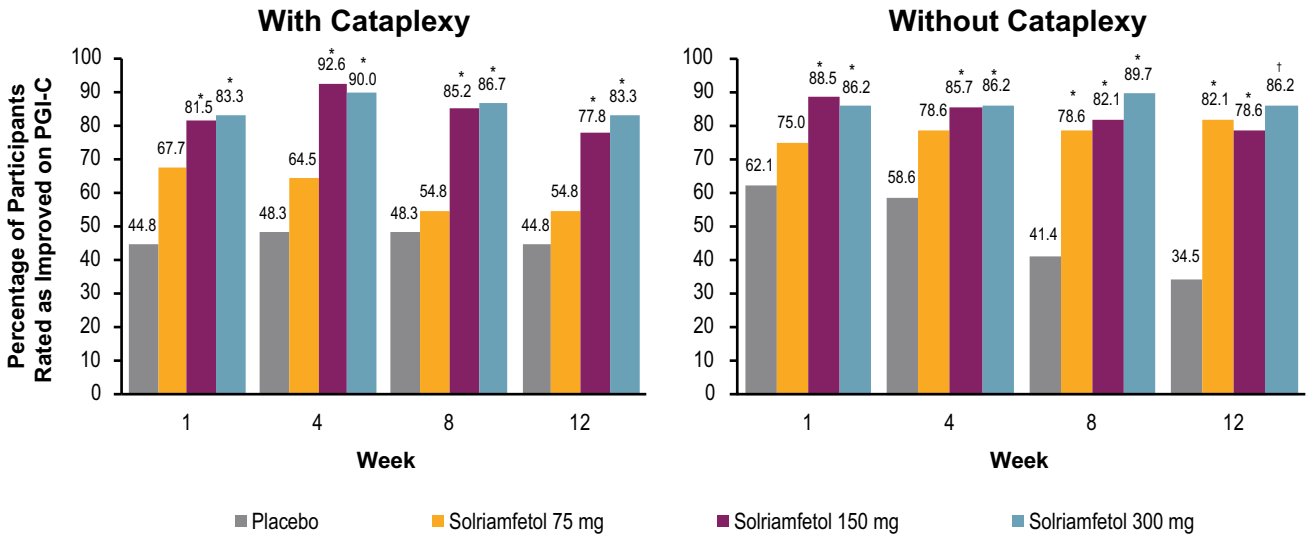


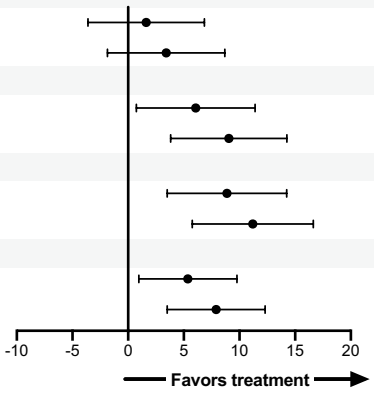

**Fig. 5** Percentages of participants with and without cataplexy reporting improvement on PGI-C from baseline to week 12. Subgroup analyses were not powered for statistical significance and not controlled for multiplicity. *$p < 0.05$ and †$p < 0.0001$ vs. placebo. With cataplexy: placebo ($n = 29$), solriamfetol 75 mg ($n = 31$), solriamfetol 150 mg ($n = 27$), solriamfetol 300 mg ($n = 30$). Without cataplexy: placebo ($n = 29$), solriamfetol 75 mg ($n = 28$), solriamfetol 150 mg ($n = 28$), solriamfetol 300 mg ($n = 29$). *PGI-C* Patient Global Impression of Change

analyses, which were adequately powered to detect between-group differences [14]. Solriamfetol had a similar safety profile in both subgroups.

Baseline characteristics were generally similar between the two subgroups, although differences in mean sleep latency on MWT and ESS scores suggested participants with cataplexy had somewhat more severe EDS at baseline than did those without cataplexy. Although it is not possible to draw definitive conclusions regarding these unadjusted comparisons of baseline differences, greater sleepiness in participants with versus those without cataplexy, which has been reported previously [9], could be explained by potential

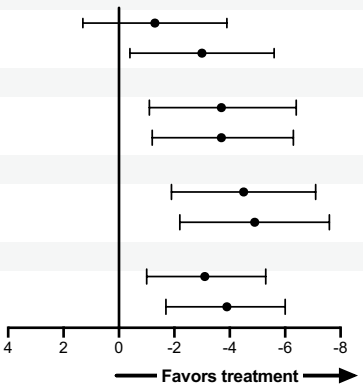
**a**

| Group/subgroup | *n* | LS mean difference (95% CI) from placebo in change from baseline to week 12: MWT mean sleep latency, min | *P* value for interaction[a] |
|---|---|---|---|
| 75 mg | | | |
| With cataplexy | 31 | 1.63 (-3.60, 6.86) | 0.52 |
| Without cataplexy | 28 | 3.43 (-1.85, 8.70) | |
| 150 mg | | | |
| With cataplexy | 27 | 6.07 (0.74, 11.40) | 0.19 |
| Without cataplexy | 28 | 9.05 (3.83, 14.27) | |
| 300 mg | | | |
| With cataplexy | 30 | 8.87 (3.51, 14.24) | 0.55 |
| Without cataplexy | 29 | 11.20 (5.77, 16.63) | |
| Overall | | | |
| With cataplexy | 88 | 5.37 (0.97, 9.78) | 0.43 |
| Without cataplexy | 85 | 7.90 (3.51, 12.30) | |




**b**

| Group/subgroup | *n* | LS mean difference (95% CI) from placebo in change from baseline to week 12: ESS scores | *P* value for interaction[a] |
|---|---|---|---|
| 75 mg | | | |
| With cataplexy | 31 | -1.3 (-3.9, 1.3) | 0.76 |
| Without cataplexy | 28 | -3.0 (-5.6, -0.4) | |
| 150 mg | | | |
| With cataplexy | 27 | -3.7 (-6.4, -1.1) | 0.71 |
| Without cataplexy | 28 | -3.7 (-6.3, -1.2) | |
| 300 mg | | | |
| With cataplexy | 30 | -4.5 (-7.1, -1.9) | 0.84 |
| Without cataplexy | 29 | -4.9 (-7.6, -2.2) | |
| Overall | | | |
| With cataplexy | 88 | -3.1 (-5.3, -1.0) | 0.64 |
| Without cataplexy | 85 | -3.9 (-6.0, -1.7) | |




**c**

| Group/subgroup | *n* | Percentage difference (95% CI) from placebo in participants reported as improved at week 12: PGI-C, % improved | *P* value for interaction[b] |
|---|---|---|---|
| 75 mg | | | |
| With cataplexy | 31 | 10.0 (-15.18, 35.20) | 0.03 |
| Without cataplexy | 28 | 47.7 (25.29, 70.03) | |
| 150 mg | | | |
| With cataplexy | 27 | 33.0 (9.00, 56.90) | 0.57 |
| Without cataplexy | 28 | 44.1 (21.06, 67.12) | |
| 300 mg | | | |
| With cataplexy | 30 | 38.5 (16.02, 60.99) | 0.47 |
| Without cataplexy | 29 | 51.7 (30.35, 73.10) | |
| Overall | | | |
| With cataplexy | 88 | 26.8 (6.36, 47.17) | 0.11 |
| Without cataplexy | 85 | 47.9 (28.77, 66.97) | |

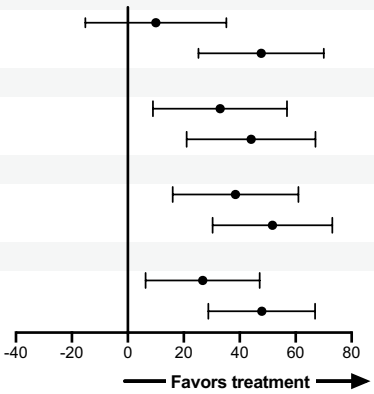



**Fig. 6** Solriamfetol treatment effects in participants with and without cataplexy. Results depicted are LS mean differences from placebo in change from baseline to week 12 on the **a** MWT and **b** ESS and **c** difference from placebo in the percentage reporting improvement on the PGI-C at week 12. Subgroup analyses were not powered for statistical significance and not controlled for multiplicity. *CI* confidence interval, *ESS* Epworth Sleepiness Scale, *LS* least squares, *MWT* Maintenance of Wakefulness Test, *PGI-C* Patient Global Impression of Change. [a]Evaluated effect modification across all visits: interaction term (treatment × visit × cataplexy status) was included in the model used for the primary analysis (a mixed-effect repeated-measures model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value). [b]Breslow–Day–Tarone test for homogeneity of odds ratio (improved/not improved) by cataplexy status at week 12

differences in pathophysiology (i.e., hypocretin deficiency [8]) and/or sleep architecture [18] between narcolepsy subtypes.

Improvement in mean sleep latency on MWT at week 12 was similar between the two subgroups. The improvement in mean sleep latency on MWT was seen for each MWT trial, reflecting an increase in sleep latency across the day with solriamfetol 150 and 300 mg in participants with or without cataplexy. Improvement in ESS scores also was similar regardless of cataplexy status. The percentage of participants with and without cataplexy who reported improvement on the PGI-C at week 12 was generally comparable, though the difference from placebo was somewhat larger in participants without cataplexy, particularly at the 75-mg dose (nominal interaction $p = 0.03$ for the 75-mg dose group only).

Overall, the comparisons by cataplexy status demonstrate that the magnitude of treatment effect on ESS and PGI-C was consistent across the subgroups for the 150- and 300-mg dose groups. In the 75-mg dose group, effects were similar or somewhat smaller in participants with versus without cataplexy; a similar pattern was also observed on the MWT for the 150- and 300-mg groups. However, there was substantial overlap across the subgroups, and formal tests for interaction did not reveal differences for most comparisons, with the exception of the 75-mg dose group on the PGI-C. These findings may indicate that the differences in baseline sleepiness between the subgroups could be clinically meaningful to some extent. The differences in response observed in this study also may reflect differences in pathophysiology between narcolepsy type 1 and type 2 or a need for higher doses of solriamfetol in participants with greater severity of sleepiness. However, given the absence of control for multiple comparisons and the fact that the analyses were not adequately powered, it is not possible to draw reliable conclusions based on these findings related to baseline severity. Based on the clinical findings outlined in this analysis along with the previously published primary results [14] and prior research [13, 19], solriamfetol should be considered a treatment option for patients with narcolepsy with or without cataplexy.

The 75- and 150-mg doses (but not the 300-mg dose) were associated with a reduction in cataplexy attacks among participants with a baseline frequency of more than ten cataplexy attacks per week. However, there were no differences in the number of cataplexy attacks in participants with cataplexy in the solriamfetol group compared with the placebo group at baseline or during the treatment period. Thus, the effect of solriamfetol on cataplexy remains unclear and warrants future research.

The overall safety and tolerability profile of solriamfetol was similar in participants with and without cataplexy. The results of this study demonstrate that solriamfetol represents an important therapeutic option for patients with narcolepsy type 1 or type 2.

Limitations include the lack of adequate power to evaluate effects on cataplexy or to detect potential treatment-effect modification in the subgroup analyses. In addition, interpretation of the statistical comparisons is limited by lack of correction for multiplicity. Hypocretin levels were not assessed in this study, so it is unclear whether differences in hypocretin levels had any bearing on outcomes.

## 5 Conclusions

Data from this 12-week, double-blind, randomized controlled trial strongly indicate that solriamfetol was effective in treating EDS in participants with narcolepsy with and without cataplexy. The safety profile of solriamfetol was comparable in participants with and without cataplexy and was consistent with prior studies.

**Table 2** Changes from baseline to weeks 9–12 in weekly number of cataplexy attacks among participants with cataplexy

| Cataplexy | Change from baseline to weeks 9–12 in number of cataplexy attacks (*n*) | | | | |
|---|---|---|---|---|---|
| | Placebo | Solriamfetol | | | |
| | | 75 mg | 150 mg | 300 mg | Combined solriamfetol |
| All participants reporting cataplexy[a] | − 3.5 ± 9.8 (25) | − 5.7 ± 14.1 (24) | − 5.2 ± 9.5 (22) | 0.1 ± 15.2 (23) | − 3.6 ± 13.3 (69) |
| Frequency of cataplexy in 7 days before baseline[b] | | | | | |
| > 0 | − 4.1 ± 10.4 (22) | − 8.9 ± 16.4 (16) | − 6.8 ± 10.3 (17) | − 0.08 ± 16.8 (19) | − 5.0 ± 15.1 (52) |
| > 5 | − 7.14 ± 13.3 (12) | − 10.6 ± 17.8 (13) | − 9.91 ± 11.8 (11) | 0.29 ± 25.1 (9) | − 7.4 ± 18.5 (33) |
| > 10 | − 7.35 ± 14.7 (10) | − 11.9 ± 19.2 (11) | − 10.6 ± 12.2 (10) | 1.86 ± 31.6 (6) | − 8.38 ± 20.4 (27) |

Data are presented as mean ± standard deviation (*n*) unless otherwise indicated

[a]Includes data from participants who recorded data in cataplexy diaries during weeks 9–12

[b]Numbers for those with > 0 cataplexy episodes differ from those in the first row because not all participants who reported having cataplexy at screening recorded a cataplexy episode in the 7 days prior to baseline

**Table 3** Summary of treatment-emergent adverse events in participants with and without cataplexy

| With cataplexy | Placebo ($n=29$) | Solriamfetol | | | |
|---|---|---|---|---|---|
| | | 75 mg ($n=31$) | 150 mg ($n=30$) | 300 mg ($n=30$) | Combined solriamfetol ($n=91$) |
| Serious TEAEs | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| TEAEs leading to discontinuation | 1 (3.4) | 0 (0) | 2 (6.7) | 4 (13.3) | 6 (6.6) |
| Most common TEAEs (≥ 5%) | | | | | |
| Headache | 2 (6.9) | 3 (9.7) | 9 (30.0) | 10 (33.3) | 22 (24.2) |
| Nasopharyngitis | 1 (3.4) | 4 (12.9) | 5 (16.7) | 2 (6.7) | 11 (12.1) |
| Decreased appetite | 1 (3.4) | 2 (6.5) | 3 (10.0) | 5 (16.7) | 10 (11.0) |
| Dry mouth | 2 (6.9) | 3 (9.7) | 3 (10.0) | 3 (10.0) | 9 (9.9) |
| Nausea | 0 (0) | 1 (3.2) | 3 (10.0) | 4 (13.3) | 8 (8.8) |
| Without cataplexy | Placebo ($n=30$) | Solriamfetol | | | |
| | | 75 mg ($n=28$) | 150 mg ($n=29$) | 300 mg ($n=29$) | Combined solriamfetol ($n=86$) |
| Serious TEAEs | 0 (0) | 0 (0) | 1 (3.4) | 0 (0) | 1 (1.2) |
| TEAEs leading to discontinuation | 0 (0) | 1 (3.6) | 1 (3.4) | 1 (3.4) | 3 (3.5) |
| Most common TEAEs (≥ 5%) | | | | | |
| Headache | 1 (3.3) | 3 (10.7) | 5 (17.2) | 8 (27.6) | 16 (18.6) |
| Nausea | 1 (3.3) | 2 (7.1) | 3 (10.3) | 6 (20.7) | 11 (12.8) |
| Decreased appetite | 0 (0) | 3 (10.7) | 2 (6.9) | 4 (13.8) | 9 (10.5) |
| Anxiety | 1 (3.3) | 1 (3.6) | 2 (6.9) | 3 (10.3) | 6 (7.0) |
| Diarrhea | 1 (3.3) | 2 (7.1) | 2 (6.9) | 1 (3.4) | 5 (5.8) |
| Nasopharyngitis | 2 (6.7) | 1 (3.6) | 3 (10.3) | 1 (3.4) | 5 (5.8) |

Data are presented as *n* (%)

*TEAEs* treatment-emergent adverse events

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**Data Availability** All data generated or analyzed during this study are included in this published article and its supplementary information file.

## Compliance with Ethical Standards

**Funding** This study was funded by Jazz Pharmaceuticals. Jazz Pharmaceuticals has worldwide development, manufacturing, and commercialization rights to solriamfetol, excluding certain jurisdictions in Asia. SK Biopharmaceuticals, the discoverer of the compound (also known as SKL-N05), maintains rights in 12 Asian markets, including Korea, China, and Japan.

**Conflict of interest** Yves Dauvilliers 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, Flamel, Harmony Biosciences, Takeda, Idorsia, and Jazz Pharmaceuticals. Colin Shapiro has received research funding from the National Institutes of Health and the Canadian Institutes of Health Research and has served on the speakers' bureau for Jazz Pharmaceuticals. Geert Mayer has received honoraria from the Paul Ehrlich Institute, Germany; has served on the speakers' bureau for UCB Pharma, Sanofi, and Bioprojet; and is a board member of the International REM Sleep Behavior Study Group. Gert Jan 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. Helene Emsellem has received consultancy fees, honoraria, and/or has been a speakers' bureau member and advisory board participant for Jazz Pharmaceuticals and Vanda Pharmaceuticals; has received research funding from Jazz Pharmaceuticals, Vanda Pharmaceuticals, Eisai, Flamel (Avadel), Balance Therapeutics, Merck & Co, NightBalance, Novartis, Philips Respironics, Idorsia Pharmaceuticals, and Harmony Biosciences; and is a board member

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**Ethics approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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