Effects of solriamfetol on on-the-road driving in participants with narcolepsy: a randomised crossover trial

Vinckenbosch, F.; Lammers, G.J.; Overeem, S.; Chen, D.; Wang, G.; Carter, L.P.; ... ; Vermeeren, A.

Received: 17 December 2021 | Revised: 24 August 2022 | Accepted: 31 October 2022

DOI: 10.1002/hup.2858

WILEY

RESEARCH ARTICLE

Effects of solriamfetol on on-the-road driving in participants with narcolepsy: A randomised crossover trial

Frederick Vinckenbosch[1] | Gert Jan Lammers[2,3] | Sebastiaan Overeem[4,5] | Dan Chen[6] | Grace Wang[6] | Lawrence P. Carter[7,8] | Kefei Zhou[6] | Johannes G. Ramaekers[1] | Annemiek Vermeeren[1]

[1]Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

[2]Sleep–Wake Centre SEIN, Leiden, The Netherlands

[3]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

[4]Sleep Medicine Center Kempenhaeghe, Heeze, The Netherlands

[5]Department of Electrical Engineering, Biomedical Diagnostics Group, Eindhoven University of Technology, Eindhoven, The Netherlands

[6]Jazz Pharmaceuticals, Palo Alto, California, USA

[7]Alector Inc, South San Francisco, California, USA

[8]University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Correspondence
Frederick Vinckenbosch, Maastricht University, PO Box 616, Maastricht, MD 6200, The Netherlands.
Email: f.vinckenbosch@maastrichtuniversity.nl

Funding information
Jazz Pharmaceuticals

Abstract

Objective: To evaluate the impact of solriamfetol, a dopamine and norepinephrine reuptake inhibitor, on on-the-road driving performance in participants with narcolepsy.

Methods: In this randomised, double-blind, placebo-controlled, crossover study, driving performance during a 1 h on-road driving test was assessed at 2 and 6 h post-dose following 7 days of treatment with solriamfetol (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or placebo. The primary endpoint was standard deviation of lateral position (SDLP) at 2 h post-dose.

Results: The study included 24 participants (54% male; mean age, 40 years); 22 had evaluable SDLP data. At 2 h post-dose, median SDLP was significantly lower (improved) with solriamfetol compared with placebo (19.08 vs. 20.46 cm [median difference, −1.9 cm], $p = 0.002$). Four participants on solriamfetol and 7 on placebo had incomplete driving tests. At 6 h post-dose, median SDLP was not statistically significantly different with solriamfetol compared with placebo (19.59 vs. 19.78 cm [median difference, −1.1 cm], $p = 0.125$). Three participants on solriamfetol and 10 on placebo had incomplete driving tests. Common adverse events (≥5%) included headache, decreased appetite, and somnolence.

Conclusions: Solriamfetol 300 mg/day improved on-the-road driving performance, at 2 h post-administration in participants with narcolepsy.

KEYWORDS
clinical trials, CNS, efficacy, neurology, pharmacotherapy

Dan Chen, Grace Wang, Lawrence P. Carter, and Kefei Zhou are former employees of Jazz Pharmaceuticals.

1 | INTRODUCTION

Narcolepsy is a chronic neurological disorder characterised by excessive daytime sleepiness (EDS) (Kornum et al., 2017; Szabo et al., 2019). Patients with narcolepsy often experience negative effects on daily functioning (Flores et al., 2016), including impaired driving performance (Findley et al., 1995; Kotterba et al., 2004). Patients with narcolepsy are also at higher risk for motor vehicle accidents (MVAs) and resulting hospitalisations (Liu et al., 2018; Philip et al., 2010; Pizza et al., 2015; Tzeng et al., 2019). For example, in a case–control study of MVAs occurring during the preceding year, the odds of having any MVA were ~3 times greater (and the odds of sleepiness-related MVA >8 times greater) in drivers with narcolepsy or hypersomnia compared with controls (Philip et al., 2010). Experimental evidence suggests that treatment with modafinil improves some measures of on-road (Philip et al., 2014) and simulated driving (Kotterba et al., 2004; Sagaspe et al., 2019) performance in patients with narcolepsy or hypersomnia. In addition, two epidemiologic studies showed that long-term treatment with modafinil or psychostimulants reduced the risk for MVAs (Pizza et al., 2015; Tzeng et al., 2019). While reduced sleep latency, as measured with the Maintenance of Wakefulness Test, has been shown to be significantly correlated with sleepiness-related MVAs and near misses in a population of patients with diverse sleep disorders (Philip et al., 2021), a reliable predictor of fitness to drive in patients with narcolepsy specifically is still lacking.

Solriamfetol (SUNOSI™, Jazz Pharmaceuticals) is a dopamine and norepinephrine reuptake inhibitor approved in the US and EU to improve wakefulness in adults with EDS associated with narcolepsy (75–150 mg/day) or obstructive sleep apnoea (OSA; 37.5–150 mg/day) (Sunosi™ (solriamfetol) tablets Prescribing Information, 2021; Sunosi™ (solriamfetol) tablets Summary of Product Characteristics, 2020). In short- (12 weeks) and long- (up to 52 weeks) term clinical trials in participants with narcolepsy, solriamfetol at doses ranging from 75 to 300 mg/day reduced EDS and improved measures of daily functioning, work productivity, and quality of life (Emsellem et al., 2020; Malhotra et al., 2020; Thorpy et al., 2019; Weaver et al., 2019).

As few randomised controlled trials have evaluated on-the-road driving performance in this population, this study was conducted to evaluate the effects of solriamfetol on on-the-road driving performance in participants with narcolepsy.

2 | METHODS

2.1 | Standard protocol approvals, registrations, and patient consents

This study (NCT 02806908; EudraCT 2015-003931-36) was conducted from July 21, 2016 to December 28, 2018 at 3 clinical sites and 1 driving test site in the Netherlands. The study protocol was approved by the medical ethics committee of University Hospital Maastricht and Maastricht University (www.toetsingonline.nl, NL56215.068.16), and all participants provided written informed consent. This study was performed in line with the International Conference on Harmonisation Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

2.2 | Participants

Participants were recruited from sleep clinics or clinical sites. Eligible participants were men and women aged 21–75 years with a diagnosis of narcolepsy, per the *International Classification of Sleep Disorders—Third Edition* (American Academy of Sleep Medicine, 2014) or the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (American Psychiatric Association, 2013). Other study inclusion criteria were average total nightly sleep ≥6 h (as verified through actigraphy and sleep diaries), body mass index 18 to <40 kg/m^2, normal vision (corrected or uncorrected), possession of a valid driver's license for ≥1 year, history of driving on a regular basis, and ability to operate a vehicle with a manual transmission.

Key exclusion criteria included occupational nighttime shift work, usual bedtime after 1:00 A.M., clinically relevant medical or psychiatric disorders (other than narcolepsy) associated with EDS, history or presence of unstable medical or psychiatric conditions, pregnancy, previous use of solriamfetol, excessive caffeine use (>8 cups of coffee/day), or smoking >10 cigarettes/day. Use of medications that affect sleep-wake functions was prohibited during the study and required a washout period prior to the first dose of study treatment (stimulants or alerting agents, 3 days; sodium oxybate, 7 days; and other medications that could affect sleep-wake functions or monoamine oxidase inhibitors, 14 days or 5 half-lives).

2.3 | Study design

This was a randomised, double-blind, placebo-controlled, 2-period crossover study of solriamfetol in participants with narcolepsy. Treatment periods consisted of 7 days of placebo or 7 days of solriamfetol (150 mg/day for 3 days, then 300 mg/day for 4 days); there was no washout between periods. This study was initiated before regulatory approval of solriamfetol or dosing recommendations were finalised; therefore, the 300-mg/day dose used here was based on prior phase 2 studies (Bogan et al., 2015; Ruoff et al., 2016) and is consistent with the maximum dose used in phase 3 trials of solriamfetol (Malhotra et al., 2020; Thorpy et al., 2019), although it exceeds the currently approved maximum dose.

2.4 | Randomisation and blinding

Eligible participants were randomly assigned 1:1 to one of treatment sequences: solriamfetol followed by placebo (solriamfetol/placebo) or placebo followed by solriamfetol (placebo/solriamfetol) (Figure 1).

Randomisation was performed by the investigator with an interactive response technology system; assignment to one treatment sequence or the other followed a blocked randomisation schedule generated by a statistician (not involved in the analysis of the study data) before the start of the study.

Solriamfetol 150- and 300 mg tablets and placebo tablets were supplied in identical opaque gelatin capsules to ensure adequate blinding. All study personnel were blinded to study treatments.

2.5 | Procedures

The study included a screening/washout period of ≤5 weeks prior to the first dose of study treatment, during which eligibility was assessed (including general safety assessments), prohibited medications were washed out, and participants completed a practice driving test. Eligible participants were randomised and started taking study drug at home to ensure a steady state of 300 mg was achieved by driving test day. Participants were contacted by telephone 2 days prior to starting study treatment and on Day 1 of Period 1 to confirm their first dose of study treatment. On Day 7 and 14 (i.e., Day 7 of each period), visits were conducted to evaluate driving performance. A safety follow-up visit was conducted approximately 1 week after completion of Period 2.

On non-test days, participants were instructed to take a single capsule orally once daily, within 1 h of waking in the morning, on an empty stomach, and then to wait ≥30 min before having breakfast. Timing of administration on non-test days was not as critical as timing of administration on driving test days, as long as the study drug was taken in compliance with label instructions (Sunosi™ (solriamfetol) tablets Prescribing Information, 2021; Sunosi™ (solriamfetol) tablets Summary of Product Characteristics, 2020). On driving test days, the capsule for that day was administered at the driving test site in the presence of an investigator at 8:45 A.M. (2 h before the start of the first drive); 30 min after administration, participants received a light breakfast. Throughout the study, caffeine users were instructed to not increase their use during the study, and nicotine users were instructed to maintain a consistent level of use. In addition, on driving test days, 1 cup of black coffee was permitted prior to arrival at the test site, with no additional consumption until after the second driving test, and nicotine use was restricted to 1 cigarette on waking, with no other use until after the study procedures were completed on those days.

At the end of each treatment period, a standardised on-road driving test (Verster & Roth, 2011) was conducted at 2 h and at 6 h after administration of drug or placebo (Figure 1). For each test (~1 h in duration), participants drove a specially instrumented vehicle over a 100 km (~62 miles) primary highway circuit; they were accompanied by a licensed driving instructor with access to dual controls (brakes, clutch, accelerator). Participants were instructed to maintain both a steady lateral position between the delineated boundaries of the slower (right) traffic lane and a constant speed of 95 km/h (~59 mph). Participants were permitted to deviate from these instructions only to pass a slower vehicle, to respond to slower traffic ahead, or to exit and reenter the highway at the turnaround point (these events were removed for the purpose of data analysis by 2 experienced editors of the driving data). Vehicle speed and lateral distance to the left-lane line were continuously recorded, and the data stored on an onboard computer. The driving test could be stopped by the participant or by the accompanying driving instructor if either considered it unsafe to continue.

2.6 | Assessments and outcomes

The primary outcome assessment from the driving tests was standard deviation of lateral position (SDLP) in centimeters—a measure of "weaving" or road-tracking control (Ramaekers, 2017; Verster & Roth, 2011). For participants who did not complete the driving test, SDLP data from the part of the test that was completed were analysed, though this could have impacted the observed treatment effect on SDLP. Standard deviation of speed and number of lane drifts (defined as deviations >100 cm from the absolute lateral position within an 8 s window) were also determined from driving test data.

The Toronto Hospital Alertness Test (THAT) is a 10-item self-report questionnaire that measures perceived alertness over the previous week; scores can range from 0 to 50, with higher scores indicating greater alertness (Shapiro et al., 2006). This assessment was administered at the end of each 7 day treatment period to evaluate participants' perceived alertness throughout the treatment period. Participants completed the THAT prior to administration of study treatment at the visits on driving test days; this timing (i.e., with respect to dosing) is not expected to affect THAT scores, since the questionnaire does not measure alertness at a point in time, but over the preceding week.

Safety assessments included a physical examination, ECG, clinical laboratory tests, and assessment of adverse events (AEs).

2.7 | Statistical analyses

The primary efficacy endpoint was SDLP at 2 h post-dose; secondary efficacy endpoints included SDLP at 6 h post-dose, percentages of participants with improved or impaired driving on solriamfetol compared with placebo, standard deviation of speed, lane drifts, and THAT score.

For the primary endpoint, the null hypothesis was that mean SDLP with solriamfetol and mean SDLP with placebo were equal; the alternative hypothesis was that they were not equal. The treatment difference in mean SDLP between solriamfetol and placebo at 2 h post-dose was tested; a 5% type I error rate ($p < 0.05$) was considered statistically significant. A sample size of 30 participants would provide 90% power to detect a mean difference of 2.0 cm on the primary outcome measure of SDLP (Ramaekers et al., 2006; Verster

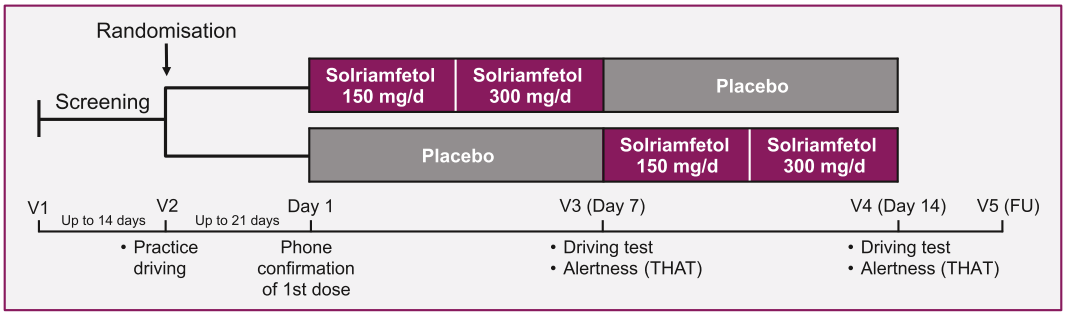

FIGURE 1 Study design. FU, follow-up; THAT, Toronto Hospital Alertness Test; V, visit

et al., 2008), assuming an SD of 3.0 cm (Verster et al., 2008) and a 2-sided 0.05 significance level using a paired *t*-test. To account for 10% dropouts without evaluable SDLP data, a sample size of 33 participants was planned. *Post hoc* calculations based on the number of enrolled participants indicated an estimated power of ~78%.

Efficacy analyses were performed with data from the modified intent-to-treat analysis population, which comprised all randomised participants who received ≥1 dose of study drug and had evaluable SDLP data at 2 h post-dose.

Change in SDLP was analysed with a repeated mixed-effects analysis of variance (ANOVA). Normality assumption was examined on the mixed effect model residuals using the Shapiro-Wilk normality test; it was observed that change in SDLP did not meet the normality assumption, and therefore the Wilcoxon signed rank test was used to compare the pairwise treatment differences.

Maximally selected McNemar symmetry analyses (Laska et al., 2012) were used to detect asymmetry in the distribution of the change in driving performance at 2 and 6 h post-dose. Single McNemar tests were used to analyse the difference in proportions of participants with improved or impaired driving performance at relevant thresholds. Thresholds of 1.0, 1.5, 2.0, 2.5, 3.0, and 3.5 cm were used. In comparisons of solriamfetol and placebo, improvement was defined as a decrease in SDLP in participants treated with solriamfetol compared to placebo at the threshold, and impairment was defined as an increase in SDLP at the threshold or failure to complete the driving test while on solriamfetol because of sleepiness or safety concerns (regardless of their performance on placebo; participants who failed to complete the driving test while on placebo but who completed the test while on solriamfetol were not counted as impaired or improved).

The number of participants who failed to complete the driving test and the duration of the drive before stopping were summarised descriptively. Additional secondary efficacy measures (standard deviation of speed, number of lane drifts, and THAT scores) were analysed using a similar ANOVA method as described for SDLP. No multiplicity adjustments were made in the efficacy analyses for multiple endpoints, and all *p* values are therefore nominal.

Demographic, narcolepsy history, and safety data were summarised for the safety population, which included all participants who received ≥1 dose of study drug. No formal statistical testing was performed on these parameters.

3 | RESULTS

A total of 29 participants were screened; of these, 4 failed screening and 25 were enrolled. One participant withdrew consent prior to dosing; therefore, 24 participants comprised the safety population. Two participants withdrew from the study and did not have evaluable SDLP data at 2 h post-dose (1 participant on placebo withdrew consent, and 1 participant on placebo withdrew due to adverse events of nausea and vomiting); therefore, the mITT population comprised 22 participants, all of whom completed the study (Figure 2).

The safety population was 54% male, with a mean age of 40.4 years; demographic and clinical characteristics (obtained from medical history) are listed in Table 1.

The observed mean (SD) SDLP at 2 h post-dose was 20.9 (3.6) cm with placebo and 19.0 (3.6) cm with solriamfetol (mean [SD] difference, −1.91 [2.5] cm) and at 6 h post-dose was 21.6 (5.8) cm and 19.8 (3.5) cm, respectively (mean [SD] difference, −1.62 [4.4] cm).

On the primary endpoint of SDLP at 2 h post-dose, the median SDLP was significantly lower with solriamfetol compared with placebo (median difference, −1.90 cm [range, −6.7 to 2.6]; $p = 0.002$); the median difference in SDLP at 6 h post-dose was −1.1 cm (range, −12.1 to 6.0; $p = 0.125$) (Table 2). SDLP differences from placebo for individual participants' data are illustrated in Figure 3a.

A total of 12 participants had ≥1 incomplete driving test. The number of incomplete driving tests was greater with placebo compared with solriamfetol at both 2 h post-dose and 6 h post-dose (Table 3). Specifically, 11 participants had ≥1 incomplete test while on placebo (6 on both tests and 5 on a single test [1 at 2 h; 4 at 6 h]) and 5 participants had ≥1 incomplete test while on solriamfetol (2 on both tests and 3 on a single test [2 at 2 h; 1 at 6 h]). For both placebo and solriamfetol, at 2 h post-dose, more tests were stopped by the instructor than by the participant; at 6 h post-dose, more tests were stopped by the participant.

Overall higher percentages of participants had improvement (vs. impairment) on solriamfetol at all thresholds (from 1.0 to 3.5 cm, except 3.5 cm at 2 h); however, single McNemar tests at each threshold did not demonstrate differences at either time point (all $p > 0.05$), and the maximum McNemar test did not show asymmetry at either 2 h (Figure 3b) or 6 h post-dose (data not shown). Individual participant data for SDLP by treatment at 2 h post-dose and 6 h post-dose are illustrated in Figure 3c,d, respectively.

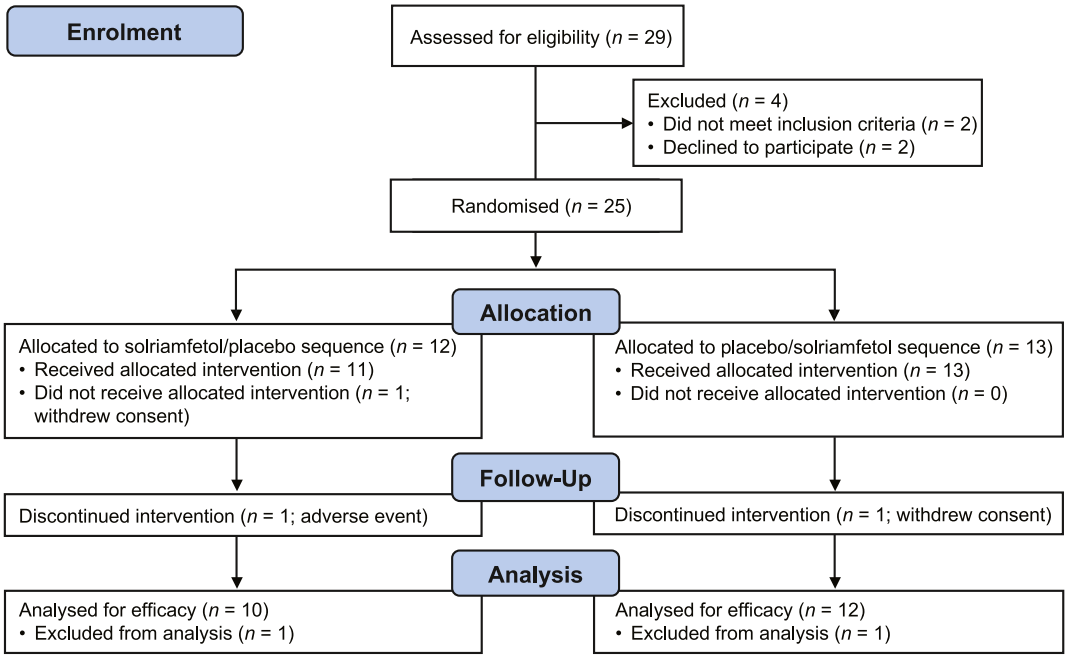

FIGURE 2 Participant disposition

TABLE 1 Demographic and baseline clinical characteristics

Characteristic	Participants (*N* = 24)
Age, years, mean (SD)	40.4 (11.8)
Male, *n* (%)	13 (54.2)
BMI, kg/m^2, mean (SD)	26.7 (5.2)
Narcolepsy history[a]	
Mean MWT sleep latency, min, mean (SD)	(*n* = 22)
	4.0 (2.5)
Presence of daily irresistible need to sleep, *n* (%)	23 (95.8)
Hypnagogic hallucinations, *n* (%)	14 (58.3)
Sleep paralysis and disruptive nighttime sleep, *n* (%)	20 (83.3)
Number of SOREM periods, mean (SD)	(*n* = 23)
	3.1 (1.1)
HLA DQB1*0602 positive, *n* (%)	21 (87.5)[b]

Abbreviations: BMI, body mass index; HLA DQB1*0602, human leukocyte antigen DQB1*0602 allele; MWT, Maintenance of Wakefulness Test; SOREM, sleep-onset rapid eye movement.

[a]Data from medical history.

[b]Data not available for 3 participants.

On the additional secondary endpoints of standard deviation of speed and number of lane drifts, no differences were observed between solriamfetol and placebo at 2 or 6 h post-dose; however, THAT scores, which measure perceived alertness over the preceding week (i.e., throughout the treatment period), were higher (indicating greater alertness) with solriamfetol compared with placebo. The least squares (LS) mean (standard error [SE]) standard deviation of speed at 2 h post-dose was 2.8 (0.2) km/h with solriamfetol and 3.0 (0.2) km/h with placebo (LS mean difference, −0.22 [95% CI: −0.48, 0.05]) and at 6 h was 3.1 (0.2) with solriamfetol and 3.2 (0.2) with placebo (LS mean difference, −0.11 [95% CI: −0.38, 0.17]). The LS mean (SE) number of lane drifts at 2 h was 2.3 (0.8) with solriamfetol and 3.3 (0.8) with placebo (LS mean difference, −0.98 [95% CI: −3.1, 1.1]) and at 6 h post-dose was 3.6 (0.8) with solriamfetol and 3.7 (0.8) with placebo (LS mean difference, −0.08 [95% CI: −2.2, 2.0]). The LS mean (SE) THAT score with placebo was 26.8 (1.4) and with solriamfetol was 34.0 (1.4), and the LS mean difference between solriamfetol and placebo was 7.1 (95% CI: 4.1, 10.2).

Treatment-emergent AEs (TEAEs) were reported for 20 (83%) participants; 6 (26%) participants experienced a TEAE while on placebo and 17 (74%) while on solriamfetol (Table 4). One participant discontinued due to AEs (nausea and vomiting, which occurred while on placebo). All TEAEs were mild or moderate in severity. The most common TEAEs reported while participants were taking solriamfetol were headache and decreased appetite (*n* = 4 each). There were no serious or fatal TEAEs. Changes from baseline in systolic and diastolic blood pressure and pulse rate were generally small, and their occurrence was proportionately similar between the 2 treatment groups and across treatment periods/visits (data not shown).

4 | DISCUSSION

This study demonstrates that solriamfetol treatment at 150 mg/day for 3 days followed by 300 mg/day for 4 days significantly improved driving performance compared with placebo in participants with narcolepsy, as determined by the primary endpoint of SDLP at 2 h

TABLE 2 Analysis of standard deviation of lateral position

	Standard deviation of lateral position					
	Placebo		Solriamfetol			
Time point	*n*	Median, cm	*n*	Median, cm	Median difference[a] (range), cm	*p*[b]
2 h post-dose[c]	22	20.46	22	19.08	−1.9 (−6.7 to 2.6)	0.002
6 h post-dose	21	19.78	22	19.59	−1.1 (−12.1 to 6.0)	0.125

[a]Solriamfetol−placebo.

[b]Wilcoxon rank sum test.

[c]Primary endpoint.

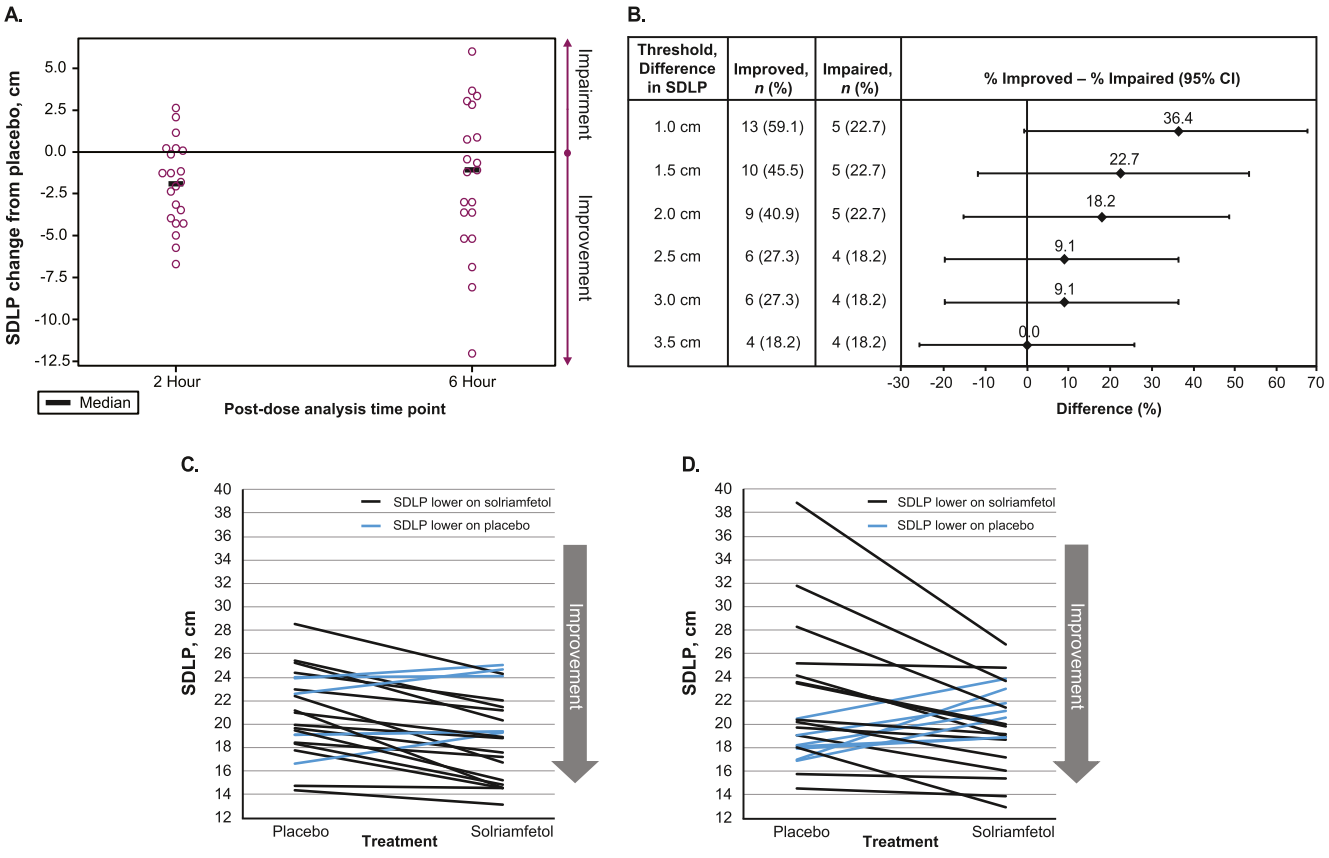

FIGURE 3 Individual driving performance and symmetry analysis. (a) standard deviation of lateral position (SDLP) difference from placebo by participant at 2 h ($n = 22$) and 6 h ($n = 21$) post-dose. (b) Symmetry analysis of SDLP difference scores at 2 h post-dose: percentage (out of $n = 22$) with improvement versus impairment of driving performance with solriamfetol compared with placebo, at thresholds increasing from 1.0 to 3.5 cm. (c) SDLP at 2 h post-dose by participant ($n = 22$). (d) SDLP at 6 h post-dose by participant ($n = 21$). SDLP, standard deviation of lateral position.

post-dose. SDLP at 6 h post-dose reflected some improvement with solriamfetol, although to a lesser extent.

While clear thresholds for clinically relevant improvement in SDLP have not been established, the clinical meaningfulness of the primary finding may be considered in the context of normative data. In an analysis of data from 74 healthy participants, the mean (SE) SDLP was 18.19 (0.46) cm with an upper limit of the 2-sided 95% CI of 19.09 cm (Vinckenbosch et al., 2021). The mean and median SDLP with placebo at 2 h post-dose in the present study (20.88 and 20.46, respectively) exceeded this threshold, suggesting impairment in this population while on placebo, whereas the mean and median SDLP with solriamfetol (18.97 and 19.08, respectively) was within the CI of the aforementioned population of healthy participants, suggesting weaving and road-tracking ability within a healthy population norm while treated with solriamfetol.

Although this study was not designed to directly assess the risk of traffic accidents, studies of the effects of blood alcohol concentration and use of benzodiazepines on driving performance suggest that change in SDLP and crash risk are highly correlated and that SDLP is a valid predictor of alcohol- or drug-induced crash risk (Owens & Ramaekers, 2009). Data are lacking to confirm the predictive validity of SDLP in the context of wake-promoting agents and

TABLE 3 Incomplete driving tests

	Placebo	Solriamfetol
Number of incomplete tests		
2 h post-dose	7	4
Stopped by participant	3	1
Stopped by instructor	4	3
6 h post-dose	10	3
Stopped by participant	7	2
Stopped by instructor	3	1
Number of participants with incomplete tests[a]	11[b]	5[b]
Duration of drive before stopping, min[c]		
Mean (SD)	27.5 (14.56)	25.9 (11.45)
Median (IQR) [range]	26.0 (21, 35) [6, 54]	27.0 (16, 33) [12, 44]

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]A total of 12 participants had incomplete tests; 7 of these participants had multiple incomplete tests (ie, on both treatments and/or at multiple timepoints); of the 5 who had a single incomplete test, 4 had an incomplete test on placebo (1 at the 2-h time point and 3 at the 6-h time point) and 1 had an incomplete test on solriamfetol (at the 2-h time point).

[b]4 of these participants had at least 1 incomplete test on solriamfetol and at least 1 on placebo.

[c]Each driving test was scheduled to be ~60 min in duration.

the potential for reducing the risk for traffic accidents. However, epidemiologic studies suggest stimulant and modafinil use reduces crash risk in patients with narcolepsy (Pizza et al., 2015; Tzeng et al., 2019). Nonetheless, the on-road driving test is generally regarded as the gold standard for assessing drug-induced changes in driving performance (Jongen et al., 2017).

Few studies of narcolepsy treatments have evaluated functional outcomes such as driving. In particular, studies of the effects of wake-promoting agents on measures of on-the-road driving performance, and specifically SDLP, in patients with narcolepsy are limited (Philip et al., 2014; Sagaspe et al., 2019). In a study of modafinil in patients with narcolepsy or idiopathic hypersomnia, the reduction in mean SDLP in an on-road driving test (conducted ~1.5 h post-dose) with modafinil (400 mg/day) compared with placebo was not statistically significant (23.6 ± 0.6 vs. 24.9 ± 0.9 cm; $p = 0.06$) (Philip et al., 2014). This is in contrast to the findings of this study, which showed a statistically significant improvement in SDLP at 2 h post-dose with solriamfetol.

Several participants were unable to complete one or more driving tests, which could result in an underestimation of SDLP. The greater number of incomplete driving tests with placebo, particularly at the 6 h post-dose time point, suggests that participants had less driving difficulty while on solriamfetol treatment. This finding supports the primary endpoint as it also reflects improvement in driving performance with solriamfetol. Considering these findings in the context of data from healthy participants, the overall percentage of driving tests stopped in this study was ~28% (24/87), which is nearly 9 times higher than in previous studies with healthy volunteers (3.1%) (Verster & Roth, 2012). In this study, 40% (17/43) of tests on placebo and 16% (7/44) on solriamfetol were stopped, whereas less than 1% and ~4% of the driving tests in unmedicated healthy volunteers and patients on various potentially sedating drug treatments, respectively, were stopped in previous studies (Verster & Roth, 2012). No participants stopped driving tests in the aforementioned modafinil study (Philip et al., 2014), despite the fact that those tests covered more than twice the distance, though participants in that study were allowed to remain on anticataplectic medication in contrast to the current study. This shows that, with and without medication, a significant percentage of participants in the current study had problems maintaining alertness for up to an hour during prolonged highway driving. Interestingly, more tests were stopped by the participant than by the instructor (13 vs. 11; Table 3). By contrast, in studies with healthy volunteers the decision to stop was 3–4 times more often made by the instructor than by the participant (Verster & Roth, 2012). This suggests that participants with narcolepsy in this study seemed aware of potential impairment and were careful to avoid further risks. If participants decided to stop before effects on SDLP were detectable, the observed treatment effect on SDLP may be an underestimation of the ability of solriamfetol to improve performance in this setting. For example, if participants had not stopped their tests while on placebo, SDLP likely would have reflected greater impairment.

The SD of SDLP has been reported to range from 2.6 to 4.2 cm in healthy participants or in participants with ADHD with or without stimulant or hypnotic treatment (Vermeeren et al., 2014; Verster et al., 2008; Verster & Roth, 2011). The power calculation performed to determine the sample size required for the present study therefore assumed an SD of 3.0 cm, in line with the estimated SD for power estimation in a study of methylphenidate use in participants with attention deficit hyperactivity disorder (Verster et al., 2008).

TABLE 4 Treatment-emergent adverse events (AEs)

TEAE, *n* (%)	Placebo (*n* = 23)	Solriamfetol (*n* = 23)	Total (*N* = 24)
Participants with any TEAE	6 (26.1)	17 (73.9)	20 (83.3)
TEAEs leading to discontinuation	1 (4.3)	0	1 (4.2)
Common TEAEs[a]			
Headache	3 (13.0)	4 (17.4)	6 (25.0)
Decreased appetite	1 (4.3)	4 (17.4)	5 (20.8)
Somnolence	2 (8.7)	3 (13.0)	5 (20.8)
Sleep disorder[b]	1 (4.3)	3 (13.0)	4 (16.7)
Agitation	0	3 (13.0)	3 (12.5)
Nausea	1 (4.3)	2 (8.7)	3 (12.5)
Palpitations	0	2 (8.7)	2 (8.3)
Dizziness	1 (4.3)	1 (4.3)	2 (8.3)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Incidence ≥5% overall.

[b]Verbatim terms: worsening sleep disturbance, worsening disturbed nocturnal sleep, worsening disturbed night sleep, and increased disturbed night sleep; all 4 participants with this TEAE had a history of disruptive nighttime sleep in their narcolepsy histories.

However, the observed SD of SDLP in this study ranged from 3.5 to 5.8 cm, suggesting the study may have been underpowered to detect a difference in SDLP. Although an improvement was still detected at 2 h post-dose in participants treated with solriamfetol, it was not maintained at 6 h post-dose. These observations align with the pharmacokinetic profile of solriamfetol, which was demonstrated to have a median time to peak plasma concentration of 2 h and a mean half-life of 5.9 h in fasting conditions (3 and 6.1 h, respectively, in fed conditions) (Zomorodi et al., 2019).

Other secondary driving outcomes (standard deviation of speed and lane drifts) showed minimal differences between solriamfetol and placebo, which may be due to a relative lack of sensitivity or statistical power. Standard deviation of speed is less sensitive to changes in driving performance parameters compared with SDLP (Irwin et al., 2017; Verster & Roth, 2014). In contrast, the difference between treatments in THAT scores was more substantial and suggested greater alertness with solriamfetol. This improvement is consistent with the established wake-promoting effects of solriamfetol on other measures, such as the Epworth Sleepiness Scale and the MWT, which showed treatment differences from placebo (least squares mean) of −2.2 to −4.7 points and 2.6–10.1 min, respectively, after 12 weeks of treatment with solriamfetol at doses of 75–300 mg/day in the phase 3 trial of solriamfetol in participants with narcolepsy (Malhotra et al., 2020; Thorpy et al., 2019). These wake-promoting effects have been shown to be maintained for up to 12 months in an open-label extension study (Malhotra et al., 2020).

The tolerability profile of solriamfetol in this study is consistent with that observed in other clinical trials in participants with narcolepsy (Ruoff et al., 2016; Thorpy et al., 2019). All TEAEs were mild or moderate in severity. No participant discontinued the study due to AEs while taking solriamfetol.

One limitation of this study is the use of solriamfetol at a dose of 300 mg/day, which exceeds the maximum recommended dose of 150 mg/day. The 300 mg/day dose was selected on the basis of prior phase 2 study data (Bogan et al., 2015; Ruoff et al., 2016) and was the highest dose used in the pivotal trials of solriamfetol in participants with narcolepsy, which demonstrated efficacy at 75 mg, 150 mg, and 300 mg (Malhotra et al., 2020; Thorpy et al., 2019). It could also be argued that the current study population was not wholly representative of clinical populations because of the prohibition against using other narcolepsy treatments during the study. Although this limitation may hamper generalisability in a population that often requires polypharmacy (Thorpy & Hiller, 2017), other treatments that affect sleepiness were prohibited to isolate the effects of solriamfetol on driving performance. Solriamfetol may also be used as monotherapy for some patients with narcolepsy (Abad, 2021). Additionally, the study was underpowered due to low participant recruitment, and reasons for stopping the test were not systematically recorded. Further, there was no active comparator in this study, limiting the ability to draw comparisons with other wake-promoting agents. Finally, no adjustments were made in the efficacy analyses, limiting interpretation of statistical findings. In particular, no adjustments were made to account for different drive durations (e.g., shorter drives may leave fewer opportunities for lane drifts to occur); however, among participants who terminated the driving test early, drive durations before stopping were similar between treatment groups.

5 | CONCLUSION

Solriamfetol 300 mg/day significantly improved SDLP, an important measure of driving performance, in participants with narcolepsy at 2 h post-dose, the primary efficacy outcome. The difference in SDLP

at 6 h post-dose, a secondary outcome, was not significant. However, these findings indicate that the robust wake-promoting efficacy of solriamfetol demonstrated in clinical trials resulted in improved real-world functional performance in participants with narcolepsy.

ACKNOWLEDGEMENTS

Under the direction of the authors, Sherri D. Jones, PharmD, and Christopher Jaworski of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support for this article, which was funded by Jazz Pharmaceuticals. This study was supported by Jazz Pharmaceuticals (Dublin, Ireland). At the time the study was conducted, Jazz Pharmaceuticals had worldwide development, manufacturing, and commercialisation rights to solriamfetol, excluding certain jurisdictions in Asia. Jazz Pharmaceuticals completed the divestiture of Sunosi® (solriamfetol) to Axsome Therapeutics, Inc. in the US on May 9, 2022 and ex-US on November 14, 2022. 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

Frederick Vinckenbosch is an employee of Maastricht University. Maastricht University received financial support to conduct the present study. 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. Sebastiaan Overeem has received an unrestricted grant from UCB Pharma for research unrelated to this work and served on advisory boards for UCB Pharma and Jazz Pharmaceuticals, all paid to institution. Dan Chen, Grace Wang, Lawrence P. Carter, and Kefei Zhou are former employees of Jazz Pharmaceuticals who, in the course of their employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. Johannes G. Ramaekers has received grants from pharmaceutical industries as well as national (NWO, ZonMw) and international (EU Commission) funding bodies that are unrelated to this work. Annemiek Vermeeren is an employee of Maastricht University. Maastricht University received financial support to conduct the present study.

DATA AVAILABILITY STATEMENT

All relevant data are provided within the manuscript. Additional data may be available upon reasonable request.

ORCID

Frederick Vinckenbosch https://orcid.org/0000-0002-1767-7742

REFERENCES

Abad, V. C. (2021). Profile of solriamfetol in the management of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea: Focus on patient selection and perspectives. *Nature and Science of Sleep*, *13*, 75–91. https://doi.org/10.2147/nss.s245020

American Academy of Sleep Medicine. (2014). *International Classification of Sleep Disorders* (3rd ed.). American Academy of Sleep Medicine.

American Psychiatric Association. (2013). Narcolepsy. In *Diagnostic and statistical manual of mental disorders* (5th ed., pp. 372–378). American Psychiatric Association.

Bogan, R. K., Feldman, N., Emsellem, H. A., Rosenberg, R., Lu, Y., Bream, G., Khayrallah, M., & Lankford, D. A. (2015). Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. *Sleep Medicine*, *16*(9), 1102–1108. https://doi.org/10.1016/j.sleep.2015.05.013

Emsellem, H. A., Thorpy, M. J., Lammers, G. J., Shapiro, C. M., Mayer, G., Plazzi, G., Chen, D., Carter, L. P., Villa, K. F., Lee, L., Menno, D., Black, J., & Dauvilliers, Y. (2020). Measures of functional outcomes, work productivity, and quality of life from a randomized, phase 3 study of solriamfetol in participants with narcolepsy. *Sleep Medicine*, *67*, 128–136. https://doi.org/10.1016/j.sleep.2019.11.1250

Findley, L., Unverzagt, M., Guchu, R., Fabrizio, M., Buckner, J., & Suratt, P. (1995). Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. *Chest*, *108*(3), 619–624. https://doi.org/10.1378/chest.108.3.619

Flores, N. M., Villa, K. F., Black, J., Chervin, R. D., & Witt, E. A. (2016). The humanistic and economic burden of narcolepsy. *Journal of Clinical Sleep Medicine*, *12*(3), 401–407. https://doi.org/10.5664/jcsm.5594

Irwin, C., Iudakhina, E., Desbrow, B., & McCartney, D. (2017). Effects of acute alcohol consumption on measures of simulated driving: A systematic review and meta-analysis. *Accident Analysis & Prevention*, *102*, 248–266. https://doi.org/10.1016/j.aap.2017.03.001

Jongen, S., Vermeeren, A., van der Sluiszen, N. N., Schumacher, M. B., Theunissen, E. L., Kuypers, K. P., Vuurman, E. F. P. M., & Ramaekers, J. G. (2017). A pooled analysis of on-the-road highway driving studies in actual traffic measuring standard deviation of lateral position (i.e., "weaving") while driving at a blood alcohol concentration of 0.5 g/L. *Psychopharmacology*, *234*(5), 837–844. https://doi.org/10.1007/s00213-016-4519-z

Kornum, B. R., Knudsen, S., Ollila, H. M., Pizza, F., Jennum, P. J., Dauvilliers, Y., & Overeem, S. (2017). Narcolepsy. *Nature Reviews Disease Primers*, *3*(1), 16100. https://doi.org/10.1038/nrdp.2016.100

Kotterba, S., Mueller, N., Leidag, M., Widdig, W., Rasche, K., Malin, J. P., Schultze-Werninghaus, G., & Orth, M. (2004). Comparison of driving simulator performance and neuropsychological testing in narcolepsy. *Clinical Neurology and Neurosurgery*, *106*(4), 275–279. https://doi.org/10.1016/j.clineuro.2003.12.003

Laska, E., Meisner, M., & Wanderling, J. (2012). A maximally selected test of symmetry about zero. *Statistics in Medicine*, *31*(26), 3178–3191. https://doi.org/10.1002/sim.5384

Liu, S. Y., Perez, M. A., & Lau, N. (2018). The impact of sleep disorders on driving safety—findings from the second Strategic Highway Research Program naturalistic driving study. *Sleep*, *41*(4), 1–11. https://doi.org/10.1093/sleep/zsy023

Malhotra, A., Shapiro, C., Pepin, J. L., Hedner, J., Ahmed, M., Foldvary-Schaefer, N., Strollo, P. J., Mayer, G., Sarmiento, K., Baladi, M., Chandler, P., Lee, L., & Schwab, R. (2020). 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*, *43*(2), zsz220. https://doi.org/10.1093/sleep/zsz220

Owens, K., & Ramaekers, J. G. (2009). Drugs, driving, and models to measure driving impairment. In J. C. Verster, S. R. Pandi-Perumal, J. G. Ramaekers, & J. J. de Gier (Eds.), *Drugs, driving and traffic safety* (pp. 43–58). Birkhauser Verlag.

Philip, P., Chaufton, C., Taillard, J., Capelli, A., Coste, O., Leger, D., Moore, N., & Sagaspe, P. (2014). Modafinil improves real driving performance in patients with hypersomnia: A randomized double-blind placebo-controlled crossover clinical trial. *Sleep*, *37*(3), 483–487. https://doi.org/10.5665/sleep.3480

Philip, P., Guichard, K., Strauss, M., Léger, D., Pepin, E., Arnulf, I., Sagaspe, P., Barateau, L., Lopez, R., Taillard, J., Micoulaud-Franchi, J. A., &

Dauvilliers, Y. (2021). Maintenance of wakefulness test: How does it predict accident risk in patients with sleep disorders? *Sleep Medicine*, *77*, 249–255. https://doi.org/10.1016/j.sleep.2020.04.007

Philip, P., Sagaspe, P., Lagarde, E., Leger, D., Ohayon, M. M., Bioulac, B., Boussuge, J., & Taillard, J. (2010). Sleep disorders and accidental risk in a large group of regular registered highway drivers. *Sleep Medicine*, *11*(10), 973–979. https://doi.org/10.1016/j.sleep.2010.07.010

Pizza, F., Jaussent, I., Lopez, R., Pesenti, C., Plazzi, G., Drouot, X., Leu-Semenescu, S., Beziat, S., Arnulf, I., & Dauvilliers, Y. (2015). Car crashes and central disorders of hypersomnolence: A French study. *PLoS One*, *10*(6), e0129386. https://doi.org/10.1371/journal.pone.0129386

Ramaekers, J. G. (2017). Drugs and driving research in medicinal drug development. *Trends Pharmacological Sciences*, *38*(4), 319–321. https://doi.org/10.1016/j.tips.2017.01.006

Ramaekers, J. G., Kuypers, K. P., & Samyn, N. (2006). Stimulant effects of 3, 4-methylenedioxymethamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal. *Addiction*, *101*(11), 1614–1621. https://doi.org/10.1111/j.1360-0443.2006.01566.x

Ruoff, C., Swick, T. J., Doekel, R., Emsellem, H. A., Feldman, N. T., Rosenberg, R., Bream, G., Khayrallah, M. A., Lu, Y., & Black, J. (2016). Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: A phase 2b study. *Sleep*, *39*(7), 1379–1387. https://doi.org/10.5665/sleep.5968

Sagaspe, P., Micoulaud-Franchi, J. A., Coste, O., Leger, D., Espie, S., Davenne, D., Lopez, R., Dauvilliers, Y., & Philip, P. (2019). Maintenance of Wakefulness Test, real and simulated driving in patients with narcolepsy/hypersomnia. *Sleep Medicine*, *55*, 1–5. https://doi.org/10.1016/j.sleep.2018.02.009

Shapiro, C. M., Auch, C., Reimer, M., Kayumov, L., Heslegrave, R., Huterer, N., Driver, H., & Devins, G. M. (2006). A new approach to the construct of alertness. *Journal of Psychosomatic Research*, *60*(6), 595–603. https://doi.org/10.1016/j.jpsychores.2006.04.012

Sunosi™ (solriamfetol) tablets prescribing information. (2021). Jazz Pharmaceuticals, Inc.

Sunosi™ (solriamfetol) tablets summary of product characteristics. (2020). Jazz Pharmaceuticals Ireland Ltd.

Szabo, S. T., Thorpy, M. J., Mayer, G., Peever, J. H., & Kilduff, T. S. (2019). Neurobiological and immunogenetic aspects of narcolepsy: Implications for pharmacotherapy. *Sleep Medicine Reviews*, *43*, 23–36. https://doi.org/10.1016/j.smrv.2018.09.006

Thorpy, M. J., & Hiller, G. (2017). The medical and economic burden of narcolepsy: Implications for managed care. *Am Health Drug Benefits*, *10*(5), 233–241.

Thorpy, M. J., Shapiro, C., Mayer, G., Corser, B. C., Emsellem, H., Plazzi, G., Chen, D., Carter, L. P., Wang, H., Lu, Y., Black, J., & Dauvilliers, Y. (2019). A randomized study of solriamfetol for excessive sleepiness in narcolepsy. *Annals of Neurology*, *85*(3), 359–370. https://doi.org/10.1002/ana.25423

Tzeng, N. S., Hsing, S. C., Chung, C. H., Chang, H. A., Kao, Y. C., Mao, W. C., Yang, C. C., Kuo, T. B., Chen, T. Y., & Chien, W. C. (2019). The risk of hospitalization for motor vehicle accident injury in narcolepsy and the benefits of stimulant use: A nationwide cohort study in Taiwan. *Journal of Clinical Sleep Medicine*, *15*(6), 881–889. https://doi.org/10.5664/jcsm.7842

Vermeeren, A., Vuurman, E. F., Leufkens, T. R., Van Leeuwen, C. J., Van Oers, A. C., Laska, E., Rico, S., Steinberg, F., & Roth, T. (2014). Residual effects of low-dose sublingual zolpidem on highway driving performance the morning after middle-of-the-night use. *Sleep*, *37*(3), 489–496. https://doi.org/10.5665/sleep.3482

Verster, J. C., Bekker, E. M., de Roos, M., Minova, A., Eijken, E. J., Kooij, J. J., Buitelaar, J. K., Kenemans, J. L., Verbaten, M. N., Olivier, B., & Volkerts, E. R. (2008). Methylphenidate significantly improves driving performance of adults with attention-deficit hyperactivity disorder: A randomized crossover trial. *Journal of Psychopharmacology*, *22*(3), 230–237. https://doi.org/10.1177/0269881107082946

Verster, J. C., & Roth, T. (2011). Standard operation procedures for conducting the on-the-road driving test, and measurement of the standard deviation of lateral position (SDLP). *International Journal of General Medicine*, *4*, 359–371. https://doi.org/10.2147/ijgm.s19639

Verster, J. C., & Roth, T. (2012). The prevalence and nature of stopped on-the-road driving tests and the relationship with objective performance impairment. *Accident Analysis & Prevention*, *45*, 498–506. https://doi.org/10.1016/j.aap.2011.09.003

Verster, J. C., & Roth, T. (2014). Effects of central nervous system drugs on driving: Speed variability versus standard deviation of lateral position as outcome measure of the on-the-road driving test. *Human Psychopharmacology*, *29*(1), 19–24. https://doi.org/10.1002/hup.2377

Vinckenbosch, F. R. J., Vermeeren, A., Vuurman, E. F. P. M., van der Sluiszen, N. N. J. J. M., Verster, J. C., van de Loo, A. J. A. E., van Dijken, J. H., Veldstra, J. L., Brookhuis, K. A., De Waard, D., & Ramaekers, J. G. (2021). An explorative approach to understanding individual differences in driving performance and neurocognition in long-term benzodiazepine users. *Human Psychopharmacology*, *36*(4), e2778. https://doi.org/10.1002/hup.2778

Weaver, T. E., Pepin, J. L., Schwab, R., Shapiro, C., Hedner, J., Ahmed, M., Foldvary-Schaefer, N., Strollo, P. J., Mayer, G., Sarmiento, K., Baladi, M., Bron, M., Chandler, P., Lee, L., & Malhotra, A. (2019). Long-term effects of solriamfetol on quality of life in participants with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea [abstract 0601]. *Sleep*, *42*(suppl 1), A239. https://doi.org/10.1093/sleep/zsz067.599

Zomorodi, K., Kankam, M., & Lu, Y. (2019). A phase I, randomized, crossover, open-label study of the pharmacokinetics of solriamfetol (JZP-110) in healthy adult subjects with and without food. *Clinical Therapeutics*, *41*(2), 196–204. https://doi.org/10.1016/j.clinthera.2018.12.001

How to cite this article: Vinckenbosch, F., Lammers, G. J., Overeem, S., Chen, D., Wang, G., Carter, L. P., Zhou, K., Ramaekers, J. G., & Vermeeren, A. (2023). Effects of solriamfetol on on-the-road driving in participants with narcolepsy: A randomised crossover trial. *Human Psychopharmacology: Clinical and Experimental*, *38*(1), e2858. https://doi.org/10.1002/hup.2858