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Effects of solriamfetol on on-the-road driving performance in participants with excessive daytime sleepiness associated with obstructive sleep apnoea

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Abstract

Objective: To evaluate the impact of solriamfetol, a dopamine and norepinephrine reuptake inhibitor, on on-the-road driving in participants with excessive daytime sleepiness (EDS) associated with obstructive sleep apnoea (OSA).

Methods: Eligible participants were aged 21–75 years with OSA and EDS (Maintenance of Wakefulness Test mean sleep latency <30 minutes and Epworth Sleepiness Scale score ≥10). Participants were randomised 1:1 to solriamfetol (150 mg/day [3 days], then 300 mg/day [4 days]) or placebo for 7 days, before crossover to the other treatment paradigm. On Day 7 of each period, standardised on-road driving tests occurred (2 and 6 hours postdose). Standard deviation of lateral position (SDLP) was the primary endpoint.

Results: Solriamfetol significantly reduced SDLP at 2 (n = 34; least squares mean difference, −1.1 cm; 95% CI, −1.85, −0.32; p = 0.006) and 6 hours postdose (n = 32; least squares mean difference, −0.8 cm; 95% CI, −1.58, −0.03; p = 0.043). Two hours

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

postdose, 4 placebo-treated and 1 solriamfetol-treated participants had incomplete driving tests; 6 hours postdose, 7 and 3 participants, respectively, had incomplete tests. Common treatment-emergent adverse events included headache, nausea, and insomnia.

Conclusions: Solriamfetol 300 mg/day significantly improved on-the-road driving performance in participants with EDS associated with OSA.

KEYWORDS
excessive daytime sleepiness, obstructive sleep apnoea, on-the-road driving, solriamfetol, Sunosi

1 | INTRODUCTION

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder that is estimated to affect nearly 1 billion adults worldwide (Benjafield et al., 2019). Excessive daytime sleepiness (EDS) is a common symptom of OSA (Dongol & Williams, 2016; Pagel, 2009) and can severely impact patients' lives, causing impairments in mood, quality of life (QoL), cognitive function, work productivity, and safety (Garbarino et al., 2016; Gasa et al., 2013; Mulgrew et al., 2007; Pepin et al., 2009; Stepnowsky et al., 2019; Zhou et al., 2016). In addition, patients with OSA and EDS have ~2.5 times the risk of motor vehicle accidents compared with healthy controls (Tregear et al., 2009), and shorter sleep latency as measured with the Maintenance of Wakefulness Test (MWT) is significantly correlated with sleepiness-related motor vehicle accidents and near misses in patients with sleep disorders (Philip et al., 2021).

Primary OSA therapy, such as continuous positive airway pressure (CPAP), can reduce symptoms of EDS; nevertheless, persistence of EDS has been reported in 9% to 22% of patients, despite their use of CPAP (Gasa et al., 2013; Pepin et al., 2009). Pharmacologic treatment can complement primary airway therapy for the alleviation of residual EDS associated with OSA (Marra et al., 2019). In laboratory studies, the wake-promoting agents (WPAs) modafinil and armodafinil (approved in the United States, but not the European Union, for the treatment of persistent EDS in patients with OSA (European Medicines Agency, 2011; Nuvigil [package insert], 2018; Provigil [package insert], 2018) have been shown to improve measures of simulated driving performance (Chapman et al., 2014; Kay & Feldman, 2013; Williams et al., 2010). In a retrospective cohort study, use of methylphenidate or modafinil was associated with a 20% reduction in the risk of hospitalisation attributable to a motor vehicle accident in patients with OSA (Lin et al., 2020). However, studies demonstrating that a pharmacologic treatment can result in specific improvements in *on-the-road* driving performance in sleepy patients with OSA are lacking.

Solriamfetol (SUNOSI™) is a dopamine and norepinephrine reuptake inhibitor approved in the United States and European Union to improve wakefulness in adult patients with EDS associated with OSA (approved dose range, 37.5–150 mg/day) (Sunosi™ (solriamfetol) tablets Prescribing Information, 2021; Sunosi™ (solriamfetol) tablets Summary of Product Characteristics, 2020). Solriamfetol was investigated in participants with EDS associated with OSA in short (12 weeks) and longer-term (up to 52 weeks) clinical trials, where treatment with solriamfetol at doses ranging from 37.5 to 300 mg/day was associated with reduced EDS and improvements on measures of daily functioning, work productivity, and QoL (Malhotra et al., 2020; Schweitzer et al., 2019; Weaver et al., 2020; Weaver et al., 2019).

In parallel with the 12-week phase 3 trial, the current study was conducted to evaluate the effects of solriamfetol on on-the-road driving performance in participants with EDS associated with OSA.

2 | METHODS

This study (NCT02806895; EudraCT 2015-003930-28) was conducted from July 5, 2016 to May 28, 2019 at 4 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, NL56214.068.16), 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.

2.1 | Participants

Participants were recruited from sleep clinics or clinical sites. Eligible participants were men and women aged 21 to 75 years with a diagnosis of OSA, per the *International Classification of Sleep Disorders – Third Edition* (American Academy of Sleep Medicine, 2014) and EDS, based on mean sleep latency <30 minutes over 4 trials of the MWT at screening, as well as Epworth Sleepiness Scale (ESS) score ≥10 at baseline. Other study inclusion criteria were average total nightly sleep ≥6 hours (assessed via actigraphy and sleep diary), body mass index (BMI) 18 to <40 kg/m^2, and one of the following: use of a primary OSA therapy (eg, PAP or oral appliance) ≥1 night/week, history of ≥1 month's attempt to use a primary OSA therapy, or history of surgical intervention for OSA. Additional criteria for

inclusion were 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. As part of the inclusion criteria, participants were also required to take a practice driving test at screening, and to complete it without any safety concerns.

Key study exclusion criteria included an unwillingness to try to use a primary OSA therapy, occupational nighttime shift work, usual bedtime after 1:00 A.M., a clinically relevant medical or psychiatric disorder (other than OSA) associated with EDS, a history or presence of an unstable medical or psychiatric condition, or pregnancy. Additional exclusion criteria were excessive caffeine use (>8 cups of coffee/day), smoking >10 cigarettes/day, use of medication that could affect sleep–wake functions within 7 days before screening, use of a monoamine oxidase inhibitor within 14 days or 5 half-lives before screening, use of an investigational drug within 30 days or 5 half-lives before baseline, anticipated use of any of these substances during the study, or previous use of solriamfetol.

2.2 | Design

A randomised, double-blind, placebo-controlled, 2-period crossover study design was used. Eligible participants were randomly assigned 1:1 to receive either solriamfetol (150 mg/day for 3 days, followed by 300 mg/day for 4 days) or placebo for 7 days (Period 1) and then cross over to the other treatment for 7 days (Period 2); there was no washout between periods. Solriamfetol 150- and 300-mg tablets and placebo tablets were supplied in identical opaque gelatin capsules to ensure adequate blinding. This study was initiated before regulatory approval or dosing recommendations were finalised. Therefore, the 300-mg/day dose used was based on prior phase 2 study data (Bogan et al., 2015; Ruoff et al., 2016), consistent with the maximum dose used in pivotal trials of solriamfetol for patients with OSA (Malhotra et al., 2020; Schweitzer et al., 2019).

2.3 | Procedures

The study included a screening/washout period of ≤28 days prior to the first dose of study treatment: Eligibility was assessed (including general safety assessments; in addition, a 40-minute MWT and ESS were assessed at visit 2), prohibited medications were washed out, and participants completed a practice driving test (at baseline/visit 3). On Day 7 and 14 (ie, 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 (Figure 1a).

Participants were instructed to take a single capsule once daily, within 1 hour of waking in the morning, on an empty stomach, and then to wait ≥30 minutes before having breakfast. 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 hours before the start of the first drive); 30 minutes 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; nicotine use was restricted to 1 cigarette in the morning ≥1 hour before the first MWT trial and 1 cigarette on waking on driving test days, 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 hours and 6 hours after administration of study treatment (Figure 1b). For each test (1 hour 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 later removed for the purposes of the analysis of driving parameters by 2 experienced raters). 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.

2.4 | Assessments and outcomes

The primary outcome assessment from the driving tests was standard deviation of lateral position (SDLP) in centimetres—a measure of "weaving" or road-tracking control (Ramaekers, 2017; Verster & Roth, 2011). Data were analysed for all driving tests (completed or incomplete) with data available; for incomplete driving tests, SDLP data from the part of the test that was completed were analysed. Standard deviation of speed and number of lane drifts (defined as deviations >100 cm from the absolute lateral position within an 8-second 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 baseline and on driving test days, prior to administration of study treatment.

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

Participants using a primary OSA therapy (PAP or oral appliance) at screening recorded their primary OSA therapy usage and the estimated duration of use (more than half of the night, less than half of the night, or don't know) on a daily basis.

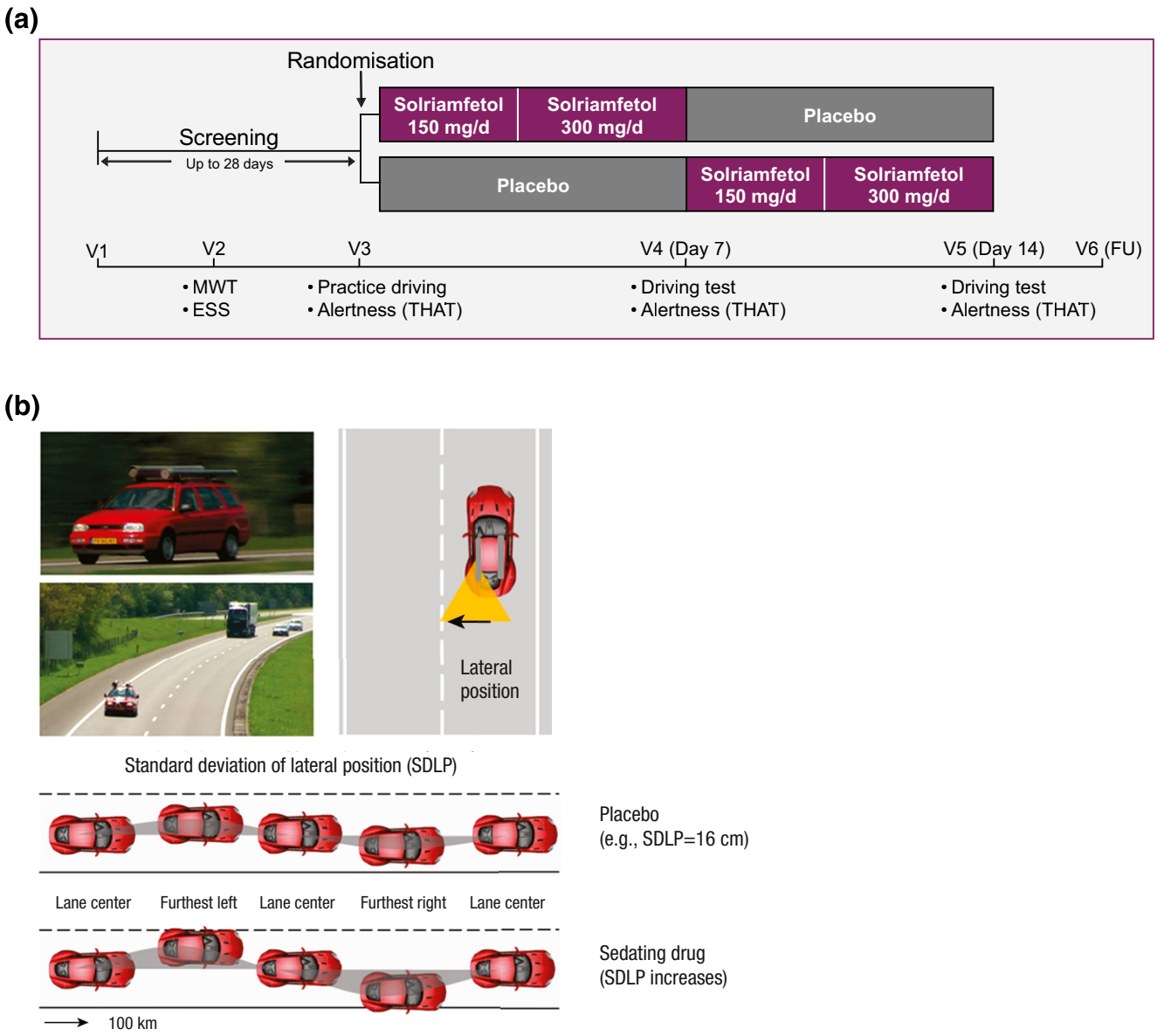

FIGURE 1 **(a)** Study design and **(b)** highway driving test. The left upper panel of Figure 1b shows the instrumented vehicle during the driving test in actual traffic on a primary highway. The lateral position of the car relative to the white middle line is continuously measured during a 1-h drive by means of a camera that is mounted on the roof of the car (right upper panel). The mean SDLP over the entire ride is calculated offline after completion of the test using signal editing software. SDLP is a measure of weaving and indicates road-tracking control of the driver. Drugs that induce sleepiness and sedation cause significant increments in weaving motion and thus loss of vehicular control. ESS, Epworth Sleepiness Scale; FU, follow-up; MWT, Maintenance of Wakefulness Test; SDLP, standard deviation of lateral position; THAT, Toronto Hospital Alertness Test; V, visit. Reprinted from *Trends in Pharmacological Sciences*, Vol. 38, No. 4, JG Ramaekers, "Drugs and Driving Research in Medicinal Drug Development," pp. 319-321, Copyright 2017, with permission from Elsevier

2.5 | Statistical analyses

The primary efficacy endpoint was SDLP at 2 hours postdose, and the secondary efficacy endpoints included SDLP at 6 hours postdose, percentage 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 at 2 hours postdose the mean SDLP values for solriamfetol and placebo were equal; the alternative hypothesis was that they were not equal. The treatment difference in mean SDLP between solriamfetol and placebo at 2 hours postdose was tested; a 5% type I error rate ($p < 0.05$) was considered statistically significant. A sample size of 36 participants would provide 90% power to detect a mean difference of 2.0 cm on the primary outcome measure, SDLP (Ramaekers et al., 2006; Verster et al., 2008), assuming a standard deviation (of SDLP) of 3.25 cm and a 2-sided 0.05 significance level using paired *t* test. A study enrolment of 40 participants was planned in order to allow for

dropouts. Because of logistical challenges (eg, long distances between clinical and driving test sites), the study was completed with 34 enrollees, with an estimated power of 88.9%.

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 hours postdose.

Mean change in SDLP was analysed with a repeated mixed effect analysis of variance (ANOVA) model with treatment (solriamfetol, placebo), time (2 hours postdose, 6 hours postdose), treatment period, treatment sequence, and treatment × time interaction as fixed effects and participant as a random effect. The 2-sided 95% CIs for changes in SDLP with solriamfetol and placebo, based on the repeated mixed effect ANOVA model, were calculated for each driving test. The assumption of normal data was examined on the residuals from the mixed effect model using the Shapiro-Wilk normality test.

Maximum McNemar symmetry analyses (Laska et al., 2012) were used to detect an asymmetry in the distribution of the change in driving performance at 2 hours and 6 hours postdose. The test examined the differences in the proportions of impaired drivers and improved drivers following treatment using a generalised sign test over all relevant thresholds. Single McNemar tests were used to analyse the difference in proportions of participants taking solriamfetol with improved or impaired driving performance compared with placebo at each relevant threshold. Thresholds of 1.0, 1.5, 2.0, 2.5, and 3.5 cm were tested (Ramaekers et al., 2006; Verster et al., 2008). In comparisons of solriamfetol and placebo, improvement was defined as a decrease in SDLP in participants treated with solriamfetol compared with 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 while on placebo (participants who failed to complete the driving test while on placebo but completed the test while on solriamfetol were not counted as impaired or improved).

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

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

3 | RESULTS

Of 59 participants who were screened, 34 met the study inclusion criteria and were enrolled (Figure 2). All participants received ≥1 dose of study treatment and comprised the safety

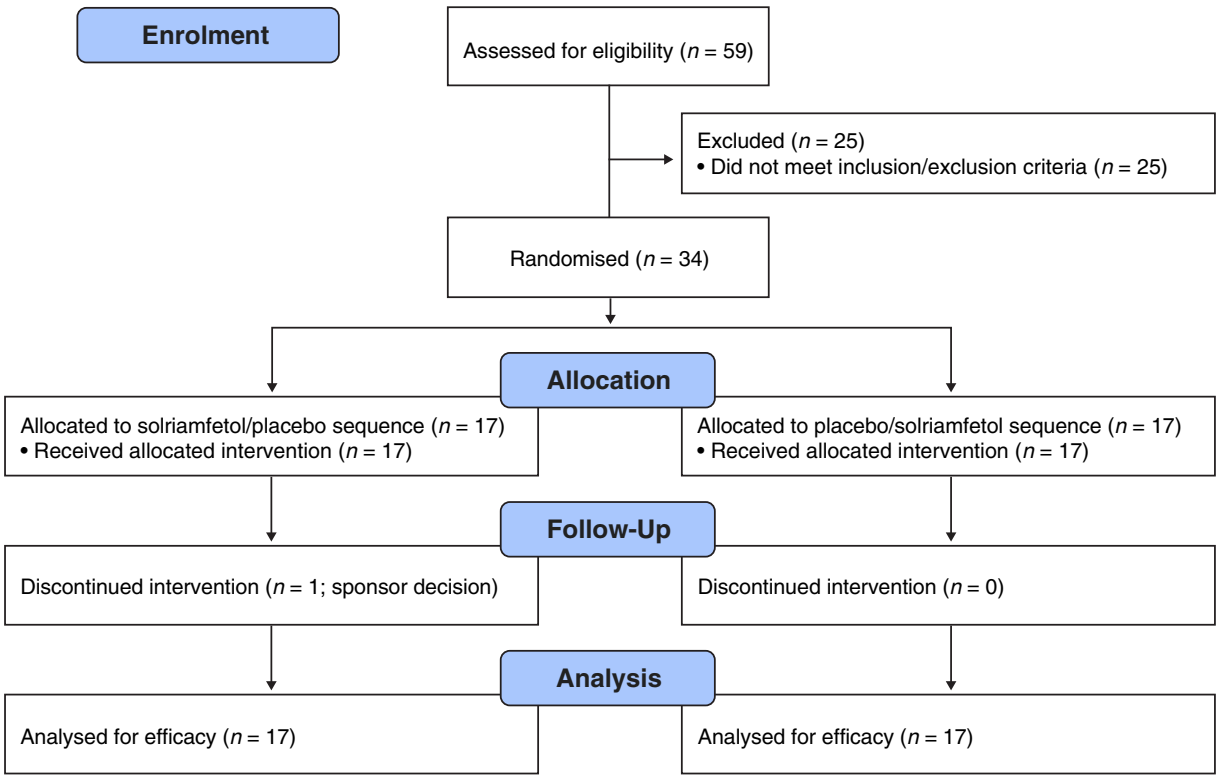

FIGURE 2 Participant disposition

population; 1 participant was withdrawn after study Period 1 and did not receive the study treatment (placebo) for Period 2. All enrolled participants were white, of non-Hispanic/Latino ethnicity, and located in the Netherlands (Table 1). Participants had a mean (standard deviation [SD]) ESS score of 14.4 (3.5) and a mean (SD) MWT sleep latency of 14.3 (7.3) minutes. Actigraphy and sleep diary data showed no differences in total sleep time between placebo and solriamfetol treatment (data not shown). Twenty-nine participants were using primary OSA therapy; the remaining 5 participants had attempted CPAP use but ultimately discontinued. Use of primary OSA therapy was stable throughout the study. The mean percentage of nights that participants used primary OSA therapy for more than half the night was 95.7% at baseline, 94.6% at the end of the placebo treatment period, and 92.7% at the end of the solriamfetol treatment period (n = 28 at each time point).

On the primary outcome measure, SDLP at 2 hours postdose, there was a statistically significant reduction with solriamfetol compared with placebo (least squares [LS] mean difference, −1.1 cm; p = 0.006; Table 2). The full set of ANOVA results is presented in Supplementary Table S1. An improvement with solriamfetol versus placebo was also observed at 6 hours postdose (LS mean difference, −0.8 cm; p = 0.043).

Individual driving performance with solriamfetol versus placebo is shown in Figure 3. Spaghetti plots of individual participant data for solriamfetol and placebo are shown in Supplementary Figure S1 for each time point.

Eight participants stopped ≥1 driving test prematurely. More participants had incomplete tests when receiving placebo compared with solriamfetol at 2 hours postdose and 6 hours postdose (Table 3). Specifically, 7 participants failed to complete ≥1 test while on placebo, and 3 failed to complete ≥1 test while on solriamfetol; 2 participants failed to complete ≥1 test on both treatments. The duration of incomplete drives ranged from 11 to 53 minutes on placebo and 28 to 51 minutes on solriamfetol. None of the participants receiving solriamfetol had their driving test halted by the instructor, compared with 2 participants receiving placebo at each time point.

Overall numerically higher percentages of participants had improvements on solriamfetol at all thresholds examined at both time points. However, the maximum McNemar test did not show asymmetry at either 2 hours (Figure 4) or 6 hours postdose (data not shown).

Secondary measures of driving performance—standard deviation of speed and lane drifts—were not different between solriamfetol and placebo at either time point (Table 4). THAT scores at the end of the treatment period were higher (indicating greater alertness) for participants receiving solriamfetol than for participants receiving placebo (27.5 vs. 23.9; LS mean difference, 3.6; p = 0.024).

Post hoc analyses were performed to examine the relationship between baseline ESS scores and MWT sleep latency and SDLP at 2 and 6 hours postdose with either treatment. Pearson correlations ranged from −0.22 to 0.14 (all $p > 0.05$), indicating no correlation between either measure of sleepiness at baseline and SDLP at the 2- or 6-hour time point for solriamfetol or placebo (Supplementary Table S2).

Treatment-emergent adverse events (TEAEs) were reported in approximately two-thirds of participants overall. The majority of TEAEs were mild to moderate in severity, and none led to study drug interruption or withdrawal. There were no serious TEAEs or deaths. The most common TEAEs were headache, nausea, insomnia, dizziness, and agitation (Table 5).

TABLE 1 Demographic and baseline clinical characteristics

Characteristic	Total (N = 34)
Age, years, mean (SD)	51.6 (12.3)
Male, n (%)	30 (88)
BMI, kg/m^2, mean (SD)	29.3 (3.9)
Use of a primary OSA therapy, n (%)	29 (85)
History of surgical intervention for OSA, n (%)	10 (29)
MWT sleep latency,[a] min, mean (SD)	14.3 (7.3)
ESS total score, mean (SD)	14.4 (3.5)
THAT total score, mean (SD) [n = 29]	26.0 (7.6)

Abbreviations: BMI, body mass index; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; OSA, obstructive sleep apnoea; SD, standard deviation; THAT, Toronto Hospital Alertness Test.
[a]For each participant, MWT sleep latency is the average of 4 trials with nonmissing values.

TABLE 2 Analysis of standard deviation of lateral position

	Standard deviation of lateral position					
	Placebo		Solriamfetol		LS mean difference[a]	
Time point	n	LS mean (SE), cm	n	LS mean (SE), cm	(95% CI), cm	p[b]
2 hours postdose[c]	33	19.9 (0.63)	34	18.8 (0.63)	−1.1 (−1.85, −0.32)	0.006
6 hours postdose	32	20.0 (0.63)	32	19.2 (0.63)	−0.8 (−1.58, −0.03)	0.043

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error.
[a]Solriamfetol − placebo.
[b]Repeated mixed effect analysis of variance (ANOVA).
[c]Primary endpoint.

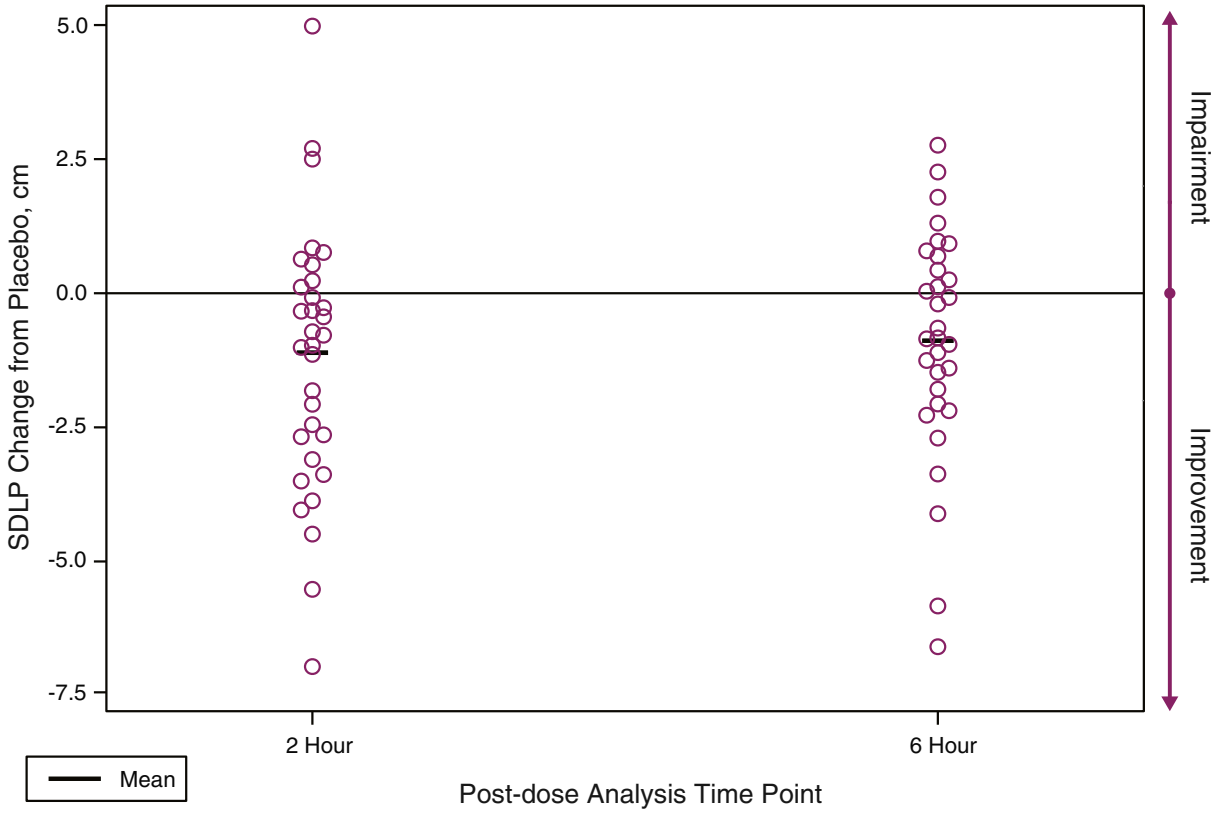

FIGURE 3 Individual driving performance with solriamfetol compared with placebo. Data for all participants, including those with incomplete driving tests. For participants who did not complete the driving test, data for the part of the drive that was completed were used to calculated SDLP. SDLP, standard deviation of lateral position

TABLE 3 Incomplete driving tests

	Placebo	Solriamfetol
Incomplete tests, *N* (*n* stopped by participant, *n* stopped by instructor)		
2 hours	4 (2, 2)	1 (1, 0)
6 hours	7 (5, 2)	3 (3, 0)
Participants, *n*, with incomplete tests[a]	7[b]	3[b]
Duration of drive before stopping, min		
Mean (SD)	33.5 (14.8)	39.0 (9.8)
Median (interquartile range)	32.0 (21, 45)	38.5 (31.5, 46.5)

Abbreviation: SD, standard deviation.

[a]Eight participants had incomplete tests; 5 of these participants had multiple incomplete tests (ie, on both treatments and/or at multiple time points); of the 3 who had a single incomplete test, 2 had an incomplete test on placebo (both at the 6-hour time point), and 1 had an incomplete test on solriamfetol (at the 6-hour time point).

[b]Two of these participants had ≥1 incomplete test on solriamfetol and ≥1 on placebo.

4 | DISCUSSION

This double-blind crossover study evaluated the effect of solriamfetol treatment on driving performance in participants with EDS associated with OSA. Participants received 7 days of treatment and undertook an on-road driving performance test 2 and 6 hours after dosing. Solriamfetol (150 mg/day for 3 days followed by 300 mg/day for 4 days) significantly improved SDLP, an important measure of driving performance, at both time points compared with placebo. Fewer participants completed the driving test on placebo than solriamfetol at both time points. Additionally, a numerically greater percentage of participants had improved SDLP than impaired SDLP with solriamfetol compared with placebo at 2 hours postdose.

Fifteen (11.5%) of 131 tests were stopped because the instructor or participant considered it unsafe to continue. This happened more frequently than in comparable studies assessing sedating drugs in healthy volunteers (3.1%) (Verster & Roth, 2012). Most incomplete tests in this study were stopped under placebo treatment (n = 11/15, 73.3%) and at the participant's request (n = 11/15, 73.3%; Table 3). In contrast, during the aforementioned studies, 3 to 4 times more tests were stopped by the instructor than the participant (Verster & Roth, 2012). This suggests that participants in our study were often aware of their potential impairment and careful to avoid further risks.

The clinical relevance of the SDLP improvement can be interpreted by comparing observed SDLP values with normative data. A study of 76 healthy participants (mean [SD] age, 55.6 [12.7] years) yielded a mean (SE) SDLP of 18.19 (0.46) cm with a 2-sided 95% CI upper bound of 19.09 cm (Vinckenbosch et al., 2021). LS mean SDLP values with placebo at 2 and 6 hours postdose in our study were 19.9 cm and 20.0 cm, respectively, indicating that sleepy participants with

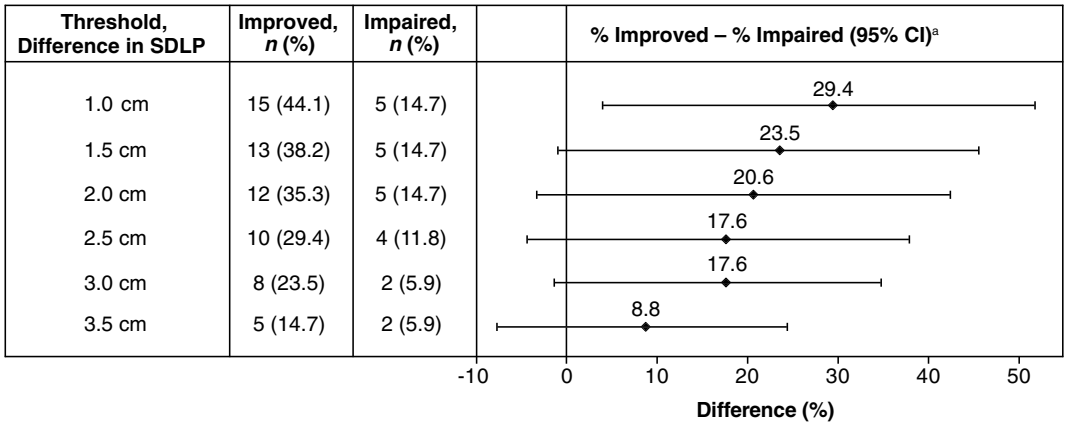

FIGURE 4 Percentage with improved vs. impaired SDLP with solriamfetol compared to placebo (2 hours postdose). Improvement and impairment based on difference in SDLP for solriamfetol versus placebo at each threshold. Percentages of participants with improvement and impairment were compared using a McNemar test to detect an asymmetry in the distribution of the change in driving performance. [a]All nominal $p > 0.05$, except nominal $p = 0.041$ at 1.0 cm at 2 hours postdose. CI, confidence interval; SDLP, standard deviation of lateral position

TABLE 4 Additional secondary endpoints

	Placebo		Solriamfetol		LS mean difference[a]	
Time point	*n*	LS mean (SE)	*n*	LS mean (SE)	(95% CI)	*p*[b]
Standard deviation of speed, km/h						
2 hours postdose	33	2.55 (0.10)	34	2.62 (0.10)	0.1 (−0.10, 0.23)	0.412
6 hours postdose	32	2.84 (0.10)	32	2.73 (0.10)	−0.1 (−0.28, 0.06)	0.199
Number of lane drifts						
2 hours postdose	33	2.89 (0.57)	34	1.76 (0.56)	−1.1 (−2.40, 0.14)	0.081
6 hours postdose	32	2.07 (0.57)	32	2.12 (0.57)	0.050 (−1.25, 1.35)	0.939
THAT (higher total score indicates greater alertness)						
End of treatment period	33	23.9 (1.2)	34	27.5 (1.2)	3.6 (0.50, 6.66)	0.024

Abbreviations: CI, confidence interval; LS, least squares; SE, standard error; THAT, Toronto Hospital Alertness Test.

[a]Solriamfetol − placebo.

[b]*p* values are nominal; standard deviation of speed and number of lane drifts were analysed using a repeated mixed effect analysis of variance (ANOVA) model; THAT scores were analysed using a mixed effect analysis of covariance (ANCOVA) model.

TABLE 5 Treatment-emergent adverse events

TEAE, *n* (%)	Placebo (*n* = 33)	Solriamfetol (*n* = 34)
Participants with any TEAE	11 (33.3)	17 (50.0)
TEAEs leading to discontinuation	0	0
Common TEAEs[a]		
Headache	4 (12.1)	5 (14.7)
Nausea	2 (6.1)	4 (11.8)
Insomnia	0	4 (11.8)
Dizziness	2 (6.1)	3 (8.8)
Agitation	1 (3.0)	1 (2.9)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Incidence ≥5% overall.

OSA receiving placebo were impaired relative to a healthy population. LS mean SDLP values 2 hours post-solriamfetol administration (18.8 cm) fell within the aforementioned 95% CI, suggesting group-level normal road-tracking performance, while LS mean SDLP 6 hours post-solriamfetol (19.2 cm) remained outside the 95% CI.

The on-road driving test is the gold standard for assessing drug-induced changes in driving (Jongen et al., 2017). However, studies with other WPAs in participants with OSA have examined only simulated driving (Chapman et al., 2014; Kay & Feldman, 2013; Williams et al., 2010). One such study in participants with OSA before CPAP initiation (Kay & Feldman, 2013) showed greater improvement with armodafinil (150 mg/day) than placebo on the Driving Safety Score (mean z-score derived from predefined safety elements, including out-of-lane driving and lane position deviation [ie, SDLP]). The absence of on-road driving data with WPAs limits comparisons of the current results to previous studies.

Consistent with its established impact on EDS, solriamfetol treatment was associated with higher THAT scores compared with placebo—indicating greater alertness. THAT has previously been found not to correlate with ESS or with the Multiple Sleep Latency Test, another objective measure of wakefulness, among sleep clinic patients (Shahid et al., 2016). This suggests that alertness (as measured by THAT) and wakefulness are distinct constructs. In a 12-week phase 3 study of participants with OSA, solriamfetol at doses up to 300 mg/day significantly improved MWT sleep latency, decreased ESS scores, increased the percentage of participants reporting overall improvement on the Patient Global Impression of Change scale at 12 weeks, and improved measures of daily functioning, work productivity, and QoL compared with placebo (Schweitzer et al., 2019; Weaver et al., 2020). These improvements in wakefulness and functional outcomes were maintained for up to 52 weeks in an open-label long-term extension study (Malhotra et al., 2020; Weaver et al., 2019). Inclusion criteria for the current study were similar to those used in phase 3 studies; likewise, mean baseline MWT latency (14.3 minutes) and ESS scores (14.4) in this study were similar to those reported in the 12-week phase 3 study (MWT, 12.0-13.6 minutes; ESS score, 14.8-15.6) (Schweitzer et al., 2019). Here, the MWT and ESS were assessed only at screening/baseline to confirm eligibility; treatment effects were not examined. Baseline MWT and ESS scores did not correlate with SDLP at any time point, indicating solriamfetol's beneficial effect did not depend on baseline levels of sleepiness.

Solriamfetol's safety profile in this study was consistent with the larger 12-week and 52-week studies (Malhotra et al., 2020; Schweitzer et al., 2019). Most TEAEs were mild or moderate in severity. Headache, nausea, insomnia, and dizziness occurred more frequently with solriamfetol than placebo. No TEAEs were serious or led to treatment/study discontinuation.

Limitations include the fact that the tested dose of solriamfetol (300 mg/day) exceeds the highest recommended dose (150 mg/day). As previously noted, this study was conducted before regulatory approvals of solriamfetol in OSA, and dosing was based on previous and ongoing studies at the time this study was designed (Bogan et al., 2015; Ruoff et al., 2016; Schweitzer et al., 2019). Thus, it is unknown how the magnitude of functional improvements observed at 300 mg/day would translate to the highest approved dose (150 mg/day) in clinical practice. However, efficacy of the 150-mg and 300-mg doses in the overall OSA population in the phase 3 study was similar (Schweitzer et al., 2019). While SDLP is linked to accident risk (Ramaekers, 2017), how the functional improvements observed here might affect accident risk is unknown, as the study was not designed to directly assess this. Additionally, long-term effects on driving performance were not assessed. An open-label extension study indicated that solriamfetol's wake-promoting effects are maintained for up to 1 year (Malhotra et al., 2020); it is reasonable to expect improved driving performance would also be maintained. Finally, the study was homogeneous in terms of race and ethnicity, and the majority of participants were male, which may limit the generalisability of these findings to other groups.

Strengths of the study include the fact that participants' baseline characteristics reflected real-world OSA populations (eg, primarily male; mean age, ~51 years; mean BMI, ~29 kg/m^2) (Bailly et al., 2016; Tkacova et al., 2014). Additionally, the driving test was conducted in on-the-road traffic. The crossover design eliminated between-group differences in participant characteristics (eg, BMI, apnoea-hypopnea index, hypoxemia) that predict motor vehicle accidents in drivers with OSA (Tregear et al., 2009).

5 | CONCLUSION

For participants with EDS associated with OSA, solriamfetol treatment was associated with significant improvement in on-the-road driving performance, as assessed by SDLP at 2 hours and 6 hours postdose; additional secondary outcome measures (THAT scores) also indicated greater alertness compared with placebo. These findings demonstrate that solriamfetol's wake-promoting efficacy observed across multiple clinical trials (Malhotra et al., 2020; Schweitzer et al., 2019) is also associated with improved real-world functional performance in this study.

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CONFLICT OF INTEREST

F. Vinckenbosch is an employee of Maastricht University. Maastricht University received financial support to conduct the present study.

J. Asin has nothing to disclose.

N. de Vries has been an advisory board participant for NightBalance, a study investigator for Inspire, and a consultant for the AE Mann Foundation, Olympus, and Philips.

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H. Janssen has nothing to disclose.

G. Wang, D. Chen, L. P. Carter, and **K. 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.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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