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Original Article

Efficacy and safety of daridorexant for the treatment of insomnia disorder in women of menopausal transition age: Insights from a randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy and safety of daridorexant in women aged 47–55 years with insomnia disorder, an age group representative of the menopause transition.
Study design: In this randomized, double-blind, placebo-controlled study (NCT03545191), conducted in 10 countries between May 2018 and May 2020, 930 patients with insomnia disorder were randomized using interactive response technology (1:1:1) to receive a single film-coated tablet of daridorexant 25 mg, 50 mg, or placebo every evening for 3 months. Subgroup analyses were performed among the 117 women aged 47–55 (25 mg $n = 43$; 50 mg $n = 35$; placebo $n = 39$).
Main outcome measures: Efficacy endpoints included change from baseline to Month 3 of treatment in polysomnography-measured wake after sleep onset (WASO) and latency to persistent sleep (LPS), self-reported total sleep time (sTST), and insomnia-related daytime impairment, as recorded on the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Safety endpoints included adverse events and score on a visual analog scale for morning sleepiness. Efficacy was analyzed in all randomized subjects, and safety in all who received at least one treatment dose.
Results: At Month 3, daridorexant 50 mg vs placebo decreased WASO and LPS by a least-squares mean (LSM) of 13.8 min (95 % CI -29.0, 1.4) and 14.7 min (−30.0, 0.6) respectively, increased sTST by an LSM of 21.8 min (−3.9, 47.4) and decreased (improved) IDSIQ total score by an LSM of 4.1 (−14.4, 6.3). No marked deviations from the effect in the overall population were observed. The incidence of somnolence/fatigue was low and comparable across groups. Morning sleepiness improved in all groups.
Conclusions: These analyses suggest that daridorexant 50 mg provides benefit in sleep outcomes and daytime functioning in women aged 47–55 with insomnia disorder. Daridorexant 50 mg is well tolerated in this population, with no increased risk of next-morning sleepiness or somnolence.
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1. Introduction

The menopausal transition refers to the period surrounding the final years of a woman's reproductive life [1], typically beginning around the age of 47, although it can start earlier, and lasting, on average, for 5–8 years [2]. One of the most prevalent and burdensome yet under-researched symptoms reported by women in the menopausal transition is sleep disturbance [3,4]. Multiple factors, including hormonal changes, vasomotor symptoms (e.g. hot flushes, night sweats), psychological changes (e.g. mood symptoms, depression), development of other sleep disorders (e.g. restless leg syndrome, obstructive sleep apnea), and social demands (e.g. caregiving), may contribute, either triggering the onset of or exacerbating preexisting sleep disturbances [5]. The severity and persistence of sleep disturbance vary among women during the menopausal transition [6]. It can have a significant impact on physical and mental health, quality of life, and productivity, especially for those who experience severe sleep disturbances that meet the criteria for insomnia disorder [7]. The Diagnostic and Statistical Manual of Mental Health Disorders-5 (DSM-5) defines insomnia disorder as a subjective complaint of difficulty initiating or maintaining sleep, or early morning awakenings for at least three nights per week over a period of at least 3 months, combined with impairment of daytime functioning or significant distress [8]. Insomnia disorder affects a significant proportion (~26 %) of women during the menopausal transition [9] and thus effective treatment to improve sleep disturbances and the daytime impairments in this population of women is required.

Despite its high prevalence, insomnia disorder during the menopausal transition is often not systematically addressed and is frequently misperceived as a secondary symptom, attributed to hot flushes, rather than an independent disorder. Hormonal therapy is the principal treatment for menopausal-related symptoms [10] and while it may improve sleep symptoms for some women, for many, insomnia may remain [10] and for others with certain medical conditions, it is contraindicated [11]. Additionally, data from experimental studies indicate that nocturnal awakenings can precede hot flushes, suggesting a bidirectional relationship [12,13].

For individuals with insomnia disorder, cognitive behavioral therapy for insomnia (CBT-I) is recommended as first-line therapy [14]. For women transitioning to menopause, similar considerations should be applied as research supports CBT-I as an efficacious treatment for improving insomnia symptoms in both peri- and post-menopausal women [15,16] with and without hot flushes. If CBT-I is unavailable, ineffective, or not preferred, several pharmacotherapies are available. Clinical trials suggest that nonbenzodiazepine receptor agonists (i.e., zolpidem; eszopiclone) can improve insomnia in peri-and post-menopausal women with hot flushes [17,18]. However, a potential increased risk of serious injuries caused by sleepwalking and complex sleep behaviors with the use of these drugs led to the U.S. Federal Drug Administration issuing a black box warning [19]. The undesirable effects of many traditional sleep medications have prompted the search for newer, safer options. Natural remedies are commonly used as sleep aids [20–22] but further pre-clinical and clinical research is needed to establish their specific effects on insomnia.

Dual orexin receptor antagonists (DORAs), and specifically daridorexant, are the only class of drugs that have a grade A recommendation for long-term use in treating insomnia disorder [14] in Europe. By selectively targeting the brain's orexin system, which regulates the sleep-wake cycle, DORAs can suppress excessive wakefulness during sleep without causing broad sedation of the central nervous system or side effects commonly associated with GABA-A modulators (benzodiazepine receptor agonists). The efficacy of DORAs in women during the menopausal transition is of interest, and previous research suggests that they may improve sleep parameters in midlife women with insomnia disorder [23,24].

Daridorexant is the most recent DORA approved for the treatment of insomnia in adults aged ≥18 years [25] and is the only DORA approved in the European Union (EU) [14]. Clinical studies have shown that daridorexant improves sleep onset and sleep maintenance for up to 12 months without causing excess next-morning residual sleepiness or dependency in patients with insomnia disorder [26–28]. At the highest approved dose of 50 mg, daridorexant also improves daytime functioning compared to placebo, resulting in less daytime sleepiness and tiredness along with better mood, improved cognition and increased alertness [26–28]. Efficacy and safety are consistent across adults and older adults, and sex [26,28]. However, the specific effects of daridorexant on sleep parameters and daytime functioning in patients with insomnia disorder during the menopausal transition have not been evaluated.

Here, in a post hoc analysis of a 12-week placebo-controlled randomized study of daridorexant, we investigate for the first time the efficacy and safety of the two approved doses of daridorexant (25 mg and 50 mg) in a subgroup of women with insomnia disorder aged 47–55, an age group representative of the menopausal transition. We assess the effect of daridorexant on both polysomnographic and self-reported sleep parameters, as well as daytime functioning.

2. Methods

2.1. Study design

This post hoc analysis is based on a large ($N = 930$), phase 3, double-blind, placebo-controlled, parallel-group clinical trial in adult participants with insomnia disorder (ClinicalTrials.gov identifier NCT03545191). The study design has been previously described [26]. In brief, participants were randomly assigned (1:1:1) to receive oral daridorexant 50 mg, daridorexant 25 mg, or placebo. Randomization was stratified by age (<65 and ≥ 65 years) and treatment was allocated using an interactive response technology system. A randomization list was generated by Almac Clinical Technologies (Souderton, PA, USA) and remained confidential until after database lock. Investigational treatment and matching placebo were indistinguishable, and all treatment wallets were packaged in the same way. In the event of a medical emergency, investigators were permitted to initiate the unmasking process; no unmasking events occurred in the study.

The double-blind treatment period was preceded by a screening period (7–18 days) and a single-blind placebo run-in period (13–24 days). During the double-blind period, participants received oral daridorexant 25 mg, daridorexant 50 mg or placebo every evening for 3 months, administered as a single film-coated tablet.

The study was conducted between May 2018 and May 2020 in ten countries (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland and the USA) at 75 sites, in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice and local regulations. The protocol was approved by institutional review boards or independent ethics committees, and all patients provided written informed consent. Safety and efficacy were monitored by an independent data monitoring committee, and an independent safety monitoring board adjudicated blinded adverse events associated with narcolepsy-like symptoms or suicide or self-injury.

At baseline, Month (M)1 and M3, participants underwent two consecutive nights of polysomnography (PSG) recording in a sleep laboratory to evaluate objective sleep measures, including wake after sleep onset (WASO) and latency to persistent sleep (LPS). Throughout the study, patients were also required to complete an electronic sleep diary daily, which included a morning and evening questionnaire, morning and evening visual analog scales (VAS) and the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Patients reported their total sleep time (sTST) every morning by answering the question, "*In total, how long did you sleep last night?*"

Morning VAS collected information on the quality of sleep, depth of sleep and morning sleepiness, while the evening VAS collected

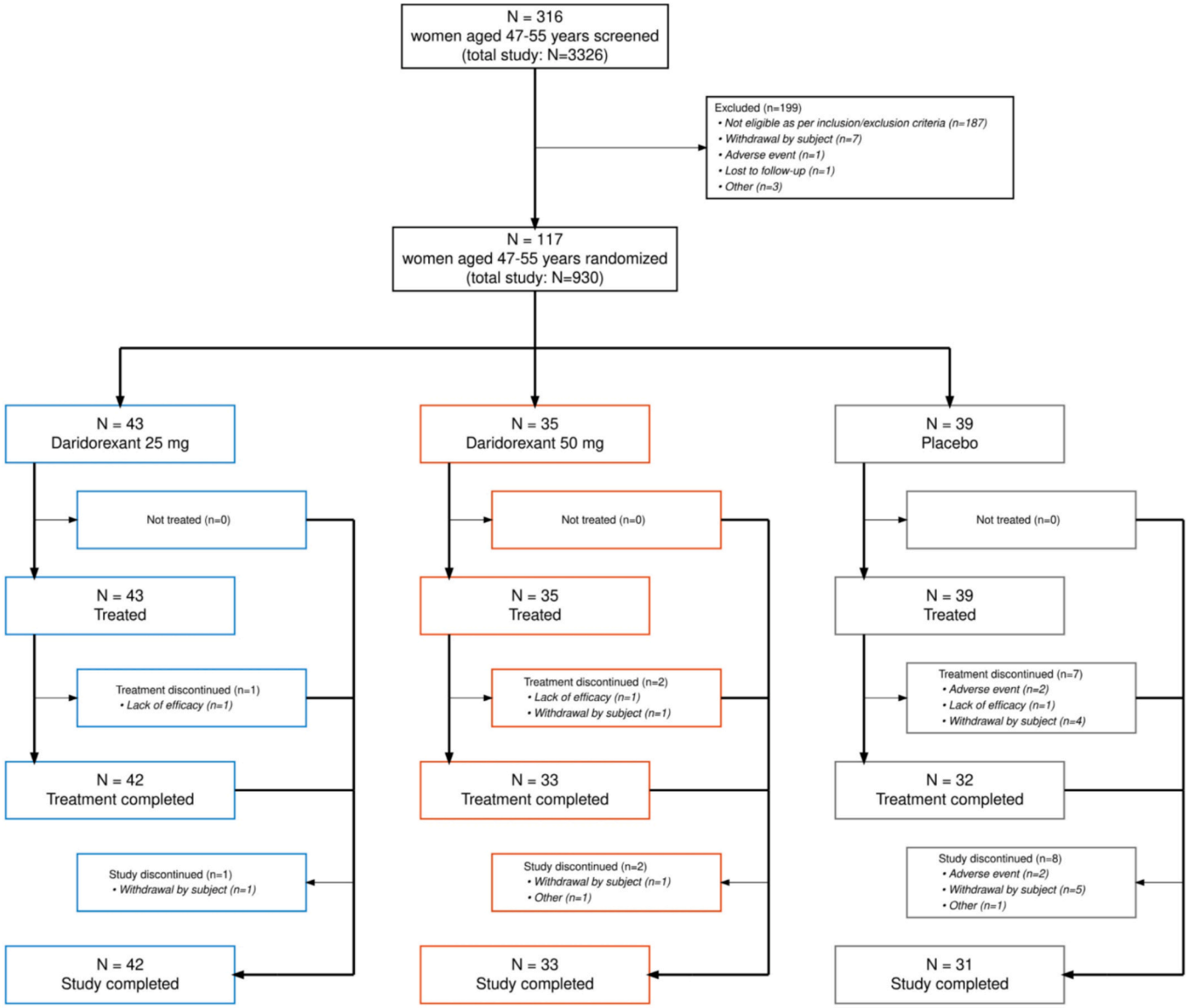

Fig. 1. Disposition of women with insomnia disorder aged 47–55 years enrolled in the study. All patients assigned to each treatment group ($N = 43$, 35 and 39 in the daridorexant 25 mg, 50 mg and placebo groups respectively) were included in the intention-to-treat analysis. All patients who received at least one dose of treatment were included in the safety population (N = 43, 35 and 39 in the daridorexant 25 mg, 50 mg and placebo groups respectively).

information on the patient's ability to function and daytime alertness. The VAS scores were each assessed on a scale from 0 to 100, with higher scores indicating better outcomes.

Every evening, participants completed the IDSIQ to self-report their daytime functioning for that day [29]. The IDSIQ is a validated instrument developed in accordance with US Food and Drug Administration guidance for determining patient-reported outcomes [29]. It contains 14 questions assessing perceived daytime functioning in subjects with insomnia disorder with a recall period of 'today'. The questions are grouped into three domains, each representing the main daytime symptoms and impacts of insomnia on sleepiness, alert/cognition and mood. The total score ranges from 0 to 140, with lower scores denoting better daytime functioning.

The Insomnia Severity Index (ISI) score, a seven-item measure for evaluating the severity and functional and emotional impacts of insomnia over the previous month, was also completed by patients at baseline, at M1, and M3. The assessment of each of the seven questions was on a 5-point scale (0–4), measuring patients' perceptions of their insomnia. The composite score, ranging from 0 to 28 points, was obtained by summing the scores from all questions. An ISI total score of 15–21 indicates a moderate level of insomnia, and a score of 22–28 indicates severe insomnia [30].

2.2. Study participants

This analysis focuses on women aged 47–55 years at baseline. The key eligibility criteria included a diagnosis of insomnia disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) [8], an ISI score $\geq$ 15 and a self-reported history of disturbed sleep ($\geq$ 30 min to fall asleep, $\geq$ 30 min awake during sleep time, sTST $\leq$ 6.5 h) for more than three nights per week for at least 3 months prior to screening. The subjective sleep quantity parameters were complemented by objective PSG-based criteria collected from two consecutive nights during the placebo run-in period to ensure the selection of patients with difficulties in both sleep onset and maintenance: LPS $\geq$ 20 min, WASO $\geq$ 30 min and total sleep time (TST) $<$ 7 h.

Key exclusion criteria included a history of sleep-related breathing disorders, any sleep disorder other than insomnia, suicide ideation/

Table 1
Baseline demographic and insomnia characteristics of women with insomnia disorder aged 47–55 years and in the overall study population.

	Daridorexant 50 mg (n = 35)	Daridorexant 25 mg (n = 43)	Placebo (n = 39)	Total subgroup population (N = 117)	Overall study population (N = 930)
Sex, female	100 %	100 %	100 %	100 %	67 %
Age at screening, years, mean (SD)	51.4 (2.6)	51.1 (2.7)	51.3 (2.8)	51.2 (2.7)	55.4 (15.3)
Race, n (%)					
White	31 (89)	38 (88)	37 (95)	106 (91)	839 (90)
Black/African	3 (9)	5 (12)	2 (5)	10 (9)	77 (8)
Asian	1 (3)	0	0	1 (1)	9 (1)
Other	0	0	0	0	5 (1)
U.S. region, n (%)	5 (14)	18 (42)	14 (36)	37 (32)	300 (32)
BMI, kg/m^2, mean (SD)	25.4 (4.2)	27.6 (4.9)	26.1 (4.2)	26.5 (4.5)	26.4 (4.3)
Time since insomnia diagnosis, years, mean (SD)	10.3 (9.0)	9.5 (9.6)	10.1 (10.0)	9.9 (9.5)	10.6 (10.4)
WASO, min, mean (SD)	97.4 (39.3)	95.5 (41.5)	88.8 (33.4)	93.9 (38.2)	98.6 (39.2)
LPS, min, mean (SD)	52.4 (29.5)	74.1 (39.4)	75.8 (35.5)	68.1 (36.6)	65.8 (38.6)
sTST, min, mean (SD)	323.2 (50.4)	295.6 (67.6)	323.8 (54.1)	313.2 (59.6)	313.0 (57.0)
IDSIQ total score[a], 0–140, mean (SD)	74.6 (21.0)	81.7 (21.2)	74.8 (21.6)	77.3 (21.4)	73.7 (24.8)
VAS scores[b], 0–100, mean (SD)					
VAS quality of sleep	34.8 (16.1)	31.0 (17.8)	36.7 (15.7)	34.0 (16.7)	35.8 (17.5)
VAS depth of sleep	34.9 (16.3)	31.6 (17.2)	37.2 (15.2)	34.4 (16.3)	36.0 (17.7)
VAS daytime alertness	41.7 (20.6)	33.4 (20.1)	39.2 (18.4)	37.8 (19.9)	39.8 (20.1)
VAS ability to function	37.9 (18.3)	32.5 (18.1)	39.9 (18.4)	36.5 (18.4)	40.2 (19.5)

BMI, body mass index; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; SD, standard deviation; sTST, self-reported total sleep time; VAS, Visual Analog Scale; WASO, wake after sleep onset.
Overall study population data previously published in Luyet, PP., Olivieri, A. & Braunstein, G. Understanding daytime functioning in insomnia: responder and correlation analyses in patients treated with daridorexant. *Sleep Science Practice* 7, 7 (2023). Used with permission under CC-CY 4.0 https://doi.org/10.1186/s41606-023-00089-x 4.0 https://creativecommons.org/licenses/by/4.0/.
[a] Lower IDSIQ total score indicate better patient-perceived daytime functioning;
[b] Higher VAS scores indicate better scores.

attempt, self-reported daytime napping (≥1 h/day ≥ 3 days/week), acute/unstable psychiatric conditions, or alcohol or drug abuse. Patients with a periodic limb movements arousal index ≥ 15/h or an apnea-hypopnea index ≥ 15 events/h during the PSG visit in the screening period were also excluded.

2.3. Efficacy endpoints

The main night-time efficacy endpoints for this analysis were change from baseline in WASO and LPS to M1 and M3 measured by PSG (primary endpoints of the phase 3 study) and change from baseline in sTST to M1 and M3 as recorded in the sleep diary (secondary endpoints of the phase 3 study). WASO and LPS values were reported as the mean of PSG recordings obtained over two consecutive nights at baseline, M1 and M3. sTST data were obtained from the mean of daily entries by participants during the 7 days before PSG nights.

Daytime functioning was assessed by the change from baseline in IDSIQ total score to M1 and M3 calculated from the mean of the daily entries during the 7 days before PSG nights at baseline, M1 and M3. The change from baseline in the VAS scores for depth and quality of sleep, ability to function and daytime alertness (mean of daily entries in the 7 days before PSG nights), and in the ISI total score to M1 and M3 were also evaluated.

2.4. Safety endpoints

Safety endpoints included treatment-emergent adverse events (TEAEs) and independent safety board-adjudicated adverse events associated with narcolepsy-like symptoms (e.g., cataplexy) or suicide/self-injury. TEAEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Morning residual effects were assessed by the morning sleepiness VAS, ranging from 0 'very sleepy' to 100 'not sleepy at all'.

2.5. Statistical analysis

In this subgroup analysis, the efficacy and safety of daridorexant 50 and 25 mg were evaluated in women aged 47–55. Randomization was not stratified for this subgroup. Efficacy analyses were based on the intention-to-treat population, defined as all participants randomized to a study treatment. Safety endpoints were analyzed in the safety analysis set defined as all participants who received at least one dose of study treatment.

Descriptive statistics are presented for all endpoints. The changes from baseline in efficacy endpoints were analyzed using a linear mixed-effects model for repeated measures. The model was adjusted for the baseline value of each endpoint, respectively, and included factors for treatment (daridorexant 50 mg and daridorexant 25 mg; placebo), visit (M1; M3), interaction of treatment by visit and baseline by visit. Missing values were assumed to be missing-at-random. Efficacy results are reported as least-squares mean (LSM) with associated standard error and 95 % CI for a change from baseline and for a difference to placebo at M1 and M3. ISI data are presented as mean (SD) only.

Results of analyses performed on the overall study population are reported in the supplementary material. If the 95 % CI of the LSM for the subgroup of women aged 47–55 years overlapped the LSM of the overall population, it was considered that there was no evidence of deviation from the overall population. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

3.1. Study population

Of the 930 participants who were randomized, 117 (12.6 %) were women aged 47–55 years and received daridorexant 50 mg (n = 35), daridorexant 25 mg (n = 43) or placebo (n = 39) (Fig. 1). Demographics in this subgroup were similar across the three treatment arms (Table 1). The mean age was 51.2 years, and most participants were White (91 %). Overall, 14 % (n = 16/117) were taking some form of concomitant hormonal therapy (therapies containing estrogens, progestogens, or with estrogen-like activity) at baseline (daridorexant 50 mg: n = 3/35; 25 mg: n = 5/43; placebo: n = 8/39).

Approximately one-third (36 %; n = 42/117) of women in this

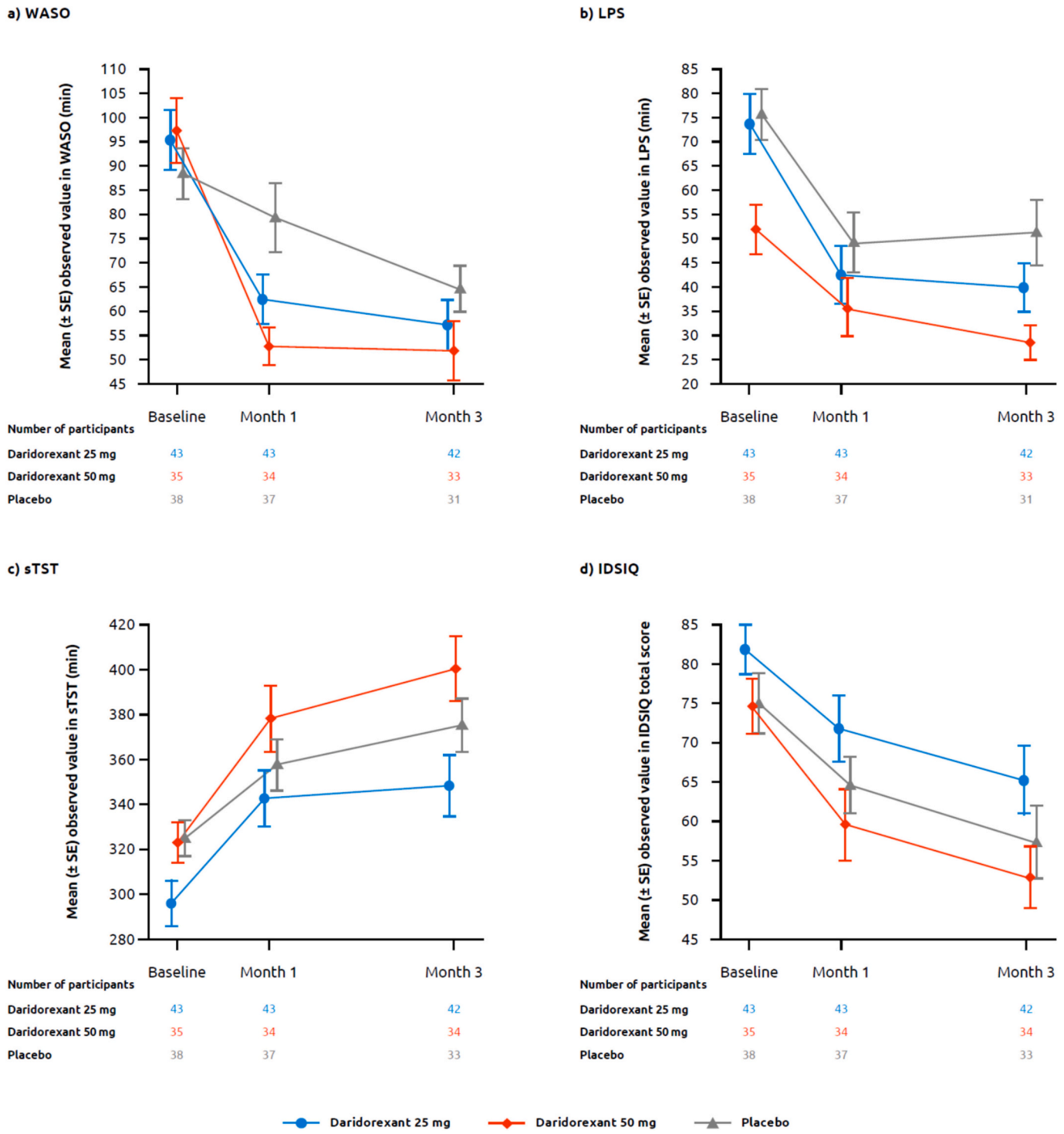

Fig. 2. Effect of daridorexant on night-time efficacy endpoints and IDSIQ total score in women with insomnia disorder aged 47–55 years. Mean of observed values for WASO (a), LPS (b), sTST (c) and IDSIQ (d) at study time points. WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Data for sTST and IDSIQ are based on the mean of daily entries in the 7 days before polysomnography nights. Lower IDSIQ scores indicate better patient-perceived daytime functioning. Error bars show SE. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; SE, standard error; sTST, self-reported total sleep time; WASO, wake after sleep onset.

subgroup were diagnosed with insomnia between the ages of 47–55 years; the remaining two-thirds (64 %; $n = 75/117$) were diagnosed before the age of 47. Baseline insomnia characteristics were generally well-balanced across treatment arms and comparable to the overall study population [26] (Table 1), except for LPS, which was numerically lower in the 50 mg group (mean 52.4 min [SD 29.5]) compared with the 25 mg (74.1 min [39.4]) and placebo (75.8 min [35.5]) groups and sTST which was numerically lower in the 25 mg group (295.6 min [67.6]) compared with the 50 mg (323.2 min [50.4]) and placebo (323.8 min [54.1]) groups.

3.2. *Night-time efficacy*

Reductions (i.e. improvement) from baseline in WASO, at M1 and

Table 2
Change from baseline in night-time and daytime efficacy measures in women with insomnia disorder aged 47–55 years.

	Month 1			Month 3		
	Daridorexant 50 mg (n = 35)	Daridorexant 25 mg (n = 43)	Placebo (n = 39)	Daridorexant 50 mg (n = 35)	Daridorexant 25 mg (n = 43)	Placebo (n = 39)
WASO, min						
LSM change from baseline (95 % CI)	−42.4 (−52.5, −32.2)	−32.0 (−41.0, −23.0)	−12.7 (−22.4, −3.0)	−42.9 (−53.5, −32.3)	−35.7 (−45.0, −26.3)	−29.1 (−40.0, −18.3)
LSM difference vs placebo (95 % CI)	−29.7 (−43.7, −15.7)	−19.4 (−32.6, −6.1)	–	−13.8 (−29.0, 1.4)	−6.6 (−20.9, 7.8)	–
LPS, min						
LSM change from baseline (95 % CI)	−23.1 (−34.2, −12.0)	−29.0 (−38.6, −19.3)	−23.3 (−33.7, −12.9)	−34.2 (−44.9, −23.5)	−31.0 (−40.2, −21.7)	−19.5 (−30.1, −8.9)
LSM difference vs placebo (95 % CI)	0.2 (−15.2, 15.6)	−5.7 (−19.8, 8.5)	–	−14.7 (−30.0, 0.6)	−11.4 (−25.4, 2.6)	–
sTST, min						
LSM change from baseline (95 % CI)	53.0 (35.3, 70.7)	47.8 (31.9, 63.7)	33.9 (17.0, 50.9)	75.3 (56.9, 93.7)	50.9 (34.3, 67.5)	53.5 (35.5, 71.6)
LSM difference vs placebo (95 % CI)	19.1 (−5.3, 43.5)	13.9 (−9.6, 37.3)	–	21.8 (−3.9, 47.4)	−2.6 (−27.3, 22.1)	–
IDSIQ total score						
LSM change from baseline (95 % CI)	−14.7 (−20.5, −8.9)	−9.6 (−14.8, −4.4)	−9.7 (−15.2, −4.1)	−21.9 (−29.3, −14.5)	−14.4 (−21.0, −7.7)	−17.8 (−25.1, −10.6)
LSM difference vs placebo (95 % CI)	−5.1 (−13.0, 2.9)	0.05 (−7.5, 7.7)	–	−4.1 (−14.4, 6.3)	3.5 (−6.4, 13.4)	–

The LSM is the adjusted mean for the baseline value of the relevant response variable, treatment (daridorexant 50 mg; daridorexant 25 mg; placebo), visit (Month 1; Month 3), interaction of treatment by visit, and baseline by visit.
CI, confidence interval; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; LSM, least square mean; SD, standard deviation; sTST, self-reported total sleep time; WASO, wake after sleep onset.

M3 were numerically greater for both daridorexant doses versus placebo, and most pronounced with daridorexant 50 mg (Fig. 2, Table 2). At M3, WASO decreased from baseline by approximately 43 min with daridorexant 50 mg and by 29 min with placebo (LSM difference: −13.8 min [95 % CI -29.0, 1.4]) (Table 2).

Improvements from baseline in LPS at M1 and M3 were observed in all groups (Fig. 2). At M3, reductions from baseline were numerically greater for both daridorexant doses and, again, most pronounced with 50 mg. At M3, LPS decreased by approximately 34 min with daridorexant 50 mg and 20 min with placebo (LSM difference: −14.7 min [95 % CI -30.0, 0.6]) (Table 2).

Improvements in sTST were larger with daridorexant 50 mg compared with 25 mg and placebo at both time points (Fig. 2, Table 2). At M3, sTST increased by approximately 75 min with daridorexant 50 mg and by 54 min with placebo (LSM difference 21.8 min [95 % CI -3.9, 47.4]) (Table 2). Improvements in sTST, particularly by M3, were not noticeably different between placebo and 25 mg. No marked deviations from the results of the overall population [26] were observed in these results on night-time sleep parameters in women aged 47–55 (Supplementary Fig. 1).

3.3. Daytime functioning: IDSIQ

In patients treated with daridorexant 50 mg, the IDSIQ total score decreased, i.e. improved, from baseline to M1 and M3 compared to placebo (Fig. 2, Table 2), indicating no marked deviation from the overall population (Supplementary Fig. 1) [26]. At M3, daridorexant 50 mg decreased IDSIQ total score by an LSM of 4.1 (95 % CI -14.4, 6.3) vs. placebo. Daridorexant 25 mg had little effect compared to placebo.

3.4. Other efficacy endpoints

Mean increases (i.e. improvements) in VAS scores for depth of sleep, quality of sleep, and ability to function (Fig. 3, Supplementary Table 2) and mean decrease in ISI score (Table 3) were numerically greater with daridorexant 50 mg compared with placebo, again consistent with the overall study population [26](Supplementary Fig. 1). Daridorexant 25 mg had little noticeable effect compared with placebo on these endpoints. Improvements in VAS daytime alertness were similar in all treatment groups, including placebo.

3.5. Safety

The prevalence of AEs was 46 % (daridorexant 50 mg), 35 % (daridorexant 25 mg) and 38 % (placebo) (Table 4). Two serious adverse events and two TEAEs leading to treatment discontinuation were reported, all within the placebo group. No deaths were reported in any of the groups. One independent safety board-adjudicated AESI was reported; this was in the placebo group and was related to excessive daytime sleepiness. TEAEs related to somnolence (50 mg: $n = 1$; 25 mg: $n = 2$; placebo: $n = 3$) and fatigue (50 mg: n = 1; 25 mg: n = 1; placebo: $n = 0$) were comparable across all groups. The VAS score for morning sleepiness increased numerically from baseline, indicating an improvement in morning sleepiness at M1 and M3 in all treatment groups (Fig. 4).

4. Discussion

This is the first study to evaluate daridorexant in a population of women with insomnia aged within the range representative of the menopausal transition. The results of this exploratory analysis suggest that daridorexant 50 mg is effective in improving both night-time sleep and daytime functioning in this population. Although no inferential statistical analyses were performed due to the small sample size and the post hoc nature of the study, the direction of changes in all efficacy parameters was toward improvement with daridorexant compared to placebo, with the highest approved dose, 50 mg, being the most efficacious. Improvements in sleep maintenance (WASO) and the quality and depth of sleep were also greater with daridorexant 50 mg versus placebo. These gains were generally notable by M1. Daridorexant was well tolerated at both doses, with no increase in next-morning sleepiness.

These efficacy and safety results, particularly for 50 mg, are generally comparable to those observed from the overall study population, which included males and females aged ≥18 years [26]. This is important in the context of the menopause transition, where there are

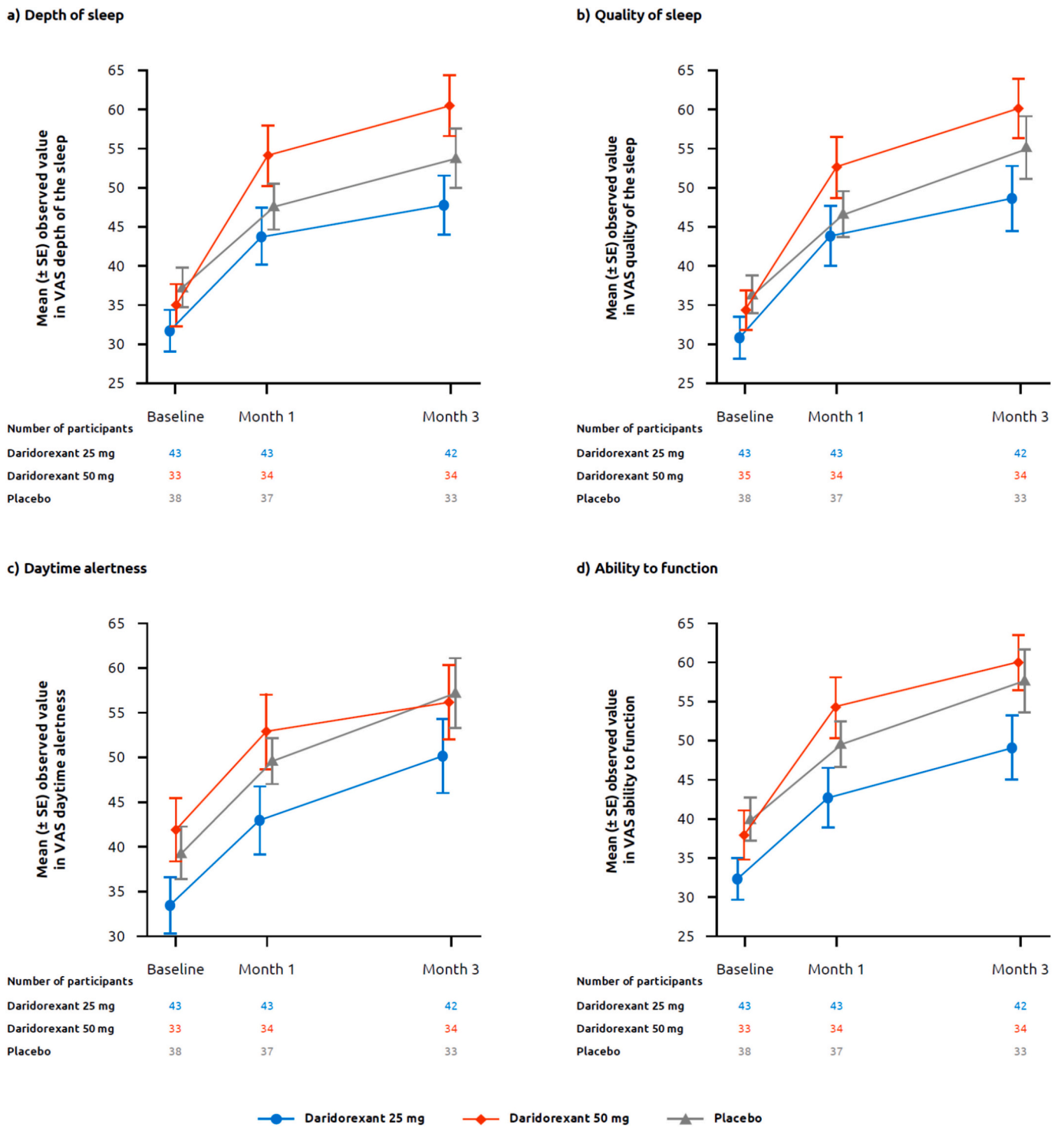

Fig. 3. Effect of daridorexant on VAS depth and quality of sleep, daytime alertness and ability to function in women with insomnia disorder aged 47–55 years. Mean of observed values for VAS a) depth of sleep, b) quality of sleep, c) daytime alertness and d) ability to function at study time points. Higher VAS scores indicate better scores. Error bars show SE. SE, standard error; VAS, visual analog scale.

additional factors (such as menopausal vascular and psychological symptoms) with the potential to disrupt sleep. However, a greater placebo response was observed in this subpopulation of women than in the overall population. While the reasons for this higher placebo response are not known, high placebo responses have also been seen in the treatment of menopausal hot flashes [31] and were similarly reported with lemborexant in midlife women with insomnia [24].

Concerning safety, daridorexant was well tolerated. Consistent with the overall study population, the effects of daridorexant were achieved without any excess morning sleepiness; rather, morning sleepiness (VAS) improved in all groups. The incidence of somnolence over the 3-month treatment period was very low in all treatment groups and similar to placebo. The somnolence rates with daridorexant in this study were lower than those reported by other DORAs in previous studies in midlife women with insomnia [23,24]. The low incidence of somnolence with daridorexant is likely attributed to its half-life of 8 h [32], which is the

Table 3
ISI score at baseline and Months 1 and 3 in women with insomnia disorder aged 47–55 years.

	Daridorexant 50 mg (n = 35)	Daridorexant 25 mg (n = 43)	Placebo (n = 39)
Baseline	19.8 (3.9)	20.7 (4.2)	19.4 (4.6)
Month 1	14.6 (7.1)	15.8 (7.0)	15.9 (5.1)
Month 3	11.8 (6.6)	14.1 (7.9)	12.8 (6.7)

ISI score data are presented as mean (SD). ISI score 0–7 = absence of insomnia; 8–14 = sub-threshold insomnia; 15–21 = moderate insomnia; and 22–28 = severe insomnia.
ISI, Insomnia Severity Index; SD, standard deviation.

Table 4
Summary of adverse events in women with insomnia disorder aged 47–55 years.

	Daridorexant 50 mg (n = 35)	Daridorexant 25 mg (n = 43)	Placebo (n = 39)
Patients with ≥1 TEAE	16 (46)	15 (35)	15 (38)
Patients with ≥1 serious TEAE	0	0	2 (5)
TEAEs leading to treatment discontinuation	0	0	2 (5)
Patients with TEAE (≥2 patients in any group)			
Nasopharyngitis	4 (11)	2 (5)	5 (13)
Headache	3 (9)	2 (5)	1 (3)
Gastroenteritis	2 (6)	1 (2)	0
Backpain	2 (6)	0	0
Influenza	2 (6)	0	0
Somnolence	1 (3)	2 (5)	3 (8)
Adjudicated AESI[a]	0	0	1 (3)

Treatment-emergent adverse events (TEAEs) that occurred during the double-blind study period up to 30 days after the double-blind study treatment end date (or the date of enrollment into the extension study) are presented with their preferred terms.
[a] Adverse events of special interest (AESI) categorized as narcolepsy-like symptoms related to excessive daytime sleepiness in a 52-year-old female: mild somnolence with onset on Day 5, no date of resolution reported. Reported to have napped during the day for an average duration of 20 min, naps were reported as involuntary.

shortest of the three DORAs. However, in the absence of direct head-to-head trials, definitive conclusions regarding comparative safety cannot be drawn.

There are limitations to this analysis that should be acknowledged and considered when interpreting the results. As this was a post hoc analysis with a small sample size, there was no statistical adjustment on multiplicity, and the results were descriptive only. Since randomization was not stratified for this subgroup, the number of patients assigned to each treatment group was not balanced and residual confounding could impact findings. The subgroup was defined only by sex, assigned at birth, and age, and thus, the actual menopause stage of each woman is unknown. Adjustment for risk factors of insomnia, such as hot flushes, was also not possible as this information was not collected. Future prospective studies of daridorexant in women with well-characterized menopausal status would help further elucidate its efficacy during the menopausal transition in women with insomnia disorder.

Given the results from this study in midlife women, it is essential that clinicians consider the diagnosis of insomnia disorder when sleep disturbances arise during the menopause transition. The DSM-5 marked a paradigm shift by moving away from viewing insomnia as merely secondary to other conditions (such as menopausal symptoms), and instead recognizing it as a disorder in its own right [8]. This reclassification broadens access to evidence-based treatments, where previously the therapeutic focus may have been limited to addressing antecedent conditions alone.

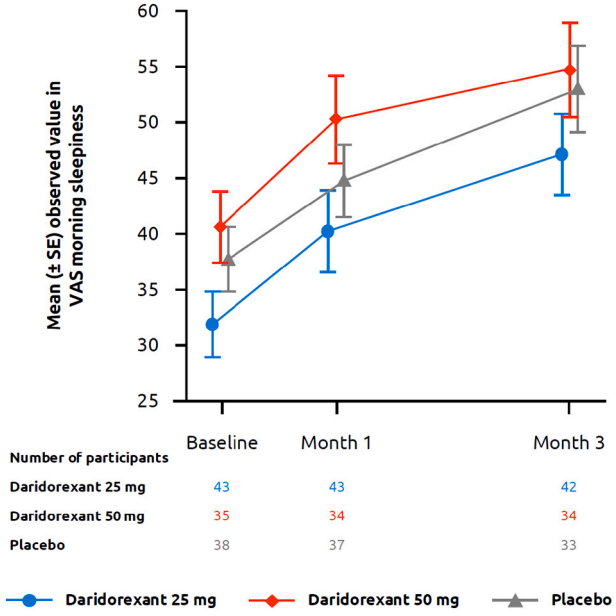

Fig. 4. Effect of daridorexant on the VAS morning sleepiness score in women with insomnia disorder aged 47–55 years.
Safety analysis set. Mean of observed values for VAS morning sleepiness score (mm) at study time points. The VAS score ranges from 0 to 100; from 0 'very sleepy' to 100 'not sleepy at all'. A higher score indicates less morning sleepiness. Error bars show SE. SE, standard error; VAS, visual analog scale.

5. Conclusion

Overall, the findings from this post hoc exploratory analysis suggest that daridorexant 50 mg provides benefits in improving both sleep outcomes and daytime functioning in women aged 47–55 years with insomnia disorder. Daridorexant 50 mg is also well tolerated in this population of women with no increased risk of next-morning sleepiness or daytime somnolence.

Contributors

All authors were involved in the conception of the analyses and in the interpretation of the data, and with review and editing of the manuscript.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Ethical approval

The study protocol was approved by the appropriate institutional review boards or independent ethics committees and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

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Data sharing and collaboration

There are no linked research data sets for this paper. The study sponsor will receive requests for individual participant data that underlie the results reported in this article, after deidentification, from researchers who provide a methodologically sound proposal. Please direct any requests to medicalinformationus@idorsia.com.

Declaration of competing interest

Zoe Schaedel has received speaker & advisory fees from Theramex, Besins, Idorsia, Astellas, Orion & Bayer.

Claudio Bassetti has served as a consultant for Idorsia Pharmaceuticals Ltd.

Petra Cassel has received lecture or expertise fees for Bayer/Jenapharm, Idorsia, Dr. Pfleger, Mementor and Frieda Health.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2025.108821.

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