Efficacy and safety of daridorexant in women with insomnia disorder during menopausal transition: a subgroup analysis

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Introduction

- During the menopausal transition, sleep disturbance is one of the most common and burdensome manifestations experienced by women,[1,2] with more than one-quarter suffering from insomnia disorder.[3]
- Insomnia disorder is characterised by difficulty initiating sleep, maintaining sleep, or frequent awakenings for at least 3 nights per week over a period of at least 3 months, combined with a significant impairment of daytime functioning.[4]
- Effective treatments are needed to improve these symptoms of insomnia disorder in this population.
- Daridorexant is a dual orexin receptor antagonist approved in the US, EU, UK, Switzerland, Canada, Japan, and Hong Kong for the treatment of insomnia in adults aged ≥ 18 years.[5]
- In a large 12-week phase 3 study comprising male and female adults with insomnia disorder, daridorexant 50 mg significantly improved objective and subjective sleep parameters and daytime functioning.[6]

Study objective

To investigate the effect of daridorexant on sleep parameters, daytime functioning and safety in women with insomnia disorder aged 47-55 years, an age group representative of the menopausal transition.

Methods

- This post hoc analysis was based on the larger (N=930) international, multicentre, double-blind, randomised, parallel-group, placebo-controlled, phase 3 study (NCT03545191) in adult patients with insomnia disorder.[6]
- Participants were randomised (1:1:1) to oral daridorexant 50 mg, 25 mg or placebo every evening for 3 months.
- Study participants were male or female adults aged ≥18 years, with insomnia disorder as per DSM-5 criteria.[4]
- Participants with a history of sleep-related breathing disorders, a history of suicide ideation/attempt or acute/unstable psychiatric conditions were excluded.

Endpoints

The endpoints assessed at Months (M) 1 and 3 in this analysis include:

- Polysomnography-measured wake after sleep onset (WASO) and latency to persistent sleep (LPS)
- Self-reported total sleep time (sTST), recorded in a sleep diary
- Insomnia-related daytime impairment, assessed using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ).
- Key safety endpoints:
  - Treatment-emergent adverse events (TEAEs)
  - Visual Analogue Scale (VAS) for morning sleepiness

Statistics

- The analysis evaluated daridorexant 50 mg and 25 mg vs placebo in the subgroup of females aged 47-55 years at screening. Randomization was not stratified for this subgroup.
- Descriptive statistics are presented for all endpoints. Efficacy data are reported as least-squares mean (LSM) with 95% CI for a change from baseline and a difference to placebo at M1 and M3. LSMs and 95% CIs from a mixed model for repeated measures with terms for treatment, visit, treatment-by-visit, baseline, and baseline-by-visit.
- Efficacy data of the subgroup were compared to the overall study population. No evidence of deviation from the overall population was considered if the 95% CI of the LSM for the subgroup overlapped the LSM of the overall population.

Results

Patients

- Of the 930 randomised participants with insomnia disorder, 117 (13%) were women aged 47-55 years (Table 1).

Table 1. Baseline characteristics of women aged 47-55 years with insomnia disorder

Mean (SD)	Daridorexant 50 mg (n=35)	Daridorexant 25 mg (n=43)	Placebo (n=39)
Age	51.4 (2.6)	51.1 (2.7)	51.3 (2.8)
Race, White, %	89%	88%	95%
Body mass index, kg/m^2	25.4 (4.2)	27.6 (4.9)	26.1 (4.2)
Time since insomnia diagnosis, years	10.3 (9.0)	9.5 (9.6)	10.1 (10.0)
WASO, min	97.4 (39.3)	95.5 (41.5)	88.8 (33.4)
LPS, min	52.4 (29.5)	74.1 (39.4)	75.8 (35.5)
sTST, min	323.2 (50.4)	295.6 (67.6)	323.8 (54.1)
Insomnia severity index score, range 0–28[a]	19.8 (3.9)	20.7 (4.2)	19.4 (4.6)
IDSIQ total score, range 0–140[b]	74.6 (21.0)	81.7 (21.2)	74.8 (21.6)

[a]15–21, moderate insomnia; 22–28, severe insomnia; [b]lower IDSIQ score indicates better patient-perceived daytime functioning

Nighttime and Daytime Efficacy (Table 2 and Figure 1)

- Both daridorexant doses improved (decreased) WASO at M1 and M3 vs placebo, with improvements most pronounced with 50 mg. Improvements in LPS (decrease) and sTST (increase) were also numerically greater at M3 with 50 mg vs placebo and 25 mg.
- Daridorexant 50 mg improved (decreased) the IDSIQ total score at M1 and M3 vs placebo. Daridorexant 25 mg had little effect vs placebo.
- No marked deviations from the results of the overall population[6] were observed (Figure 1).

Table 2. Nighttime & daytime efficacy: LSM change from baseline in sleep parameters and IDSIQ total score at M1 and M3

LSM change from baseline (95% C)		Daridorexant 50 mg (n=35)	Daridorexant 25 mg (n=43)	Placebo (n=39)
WASO, min	M1	-42.4 (-52.5, -32.2)	-32.0 (-41.0, -23.0)	-12.7 (-22.4, -3.0)
	M3	-42.9 (-53.5, -32.3)	-35.7 (-45.0, -26.3)	-29.1 (-40.0, -18.3)
LPS, min	M1	-23.1 (-34.2, -12.0)	-29.0 (-38.6, -19.3)	-23.3 (-33.7, -12.9)
	M3	-34.2 (-44.9, -23.5)	-31.0 (-40.2, -21.7)	-19.5 (-30.1, -8.9)
sTST, min	M1	53.0 (35.3, 70.7)	47.8 (31.9, 63.7)	33.9 (17.0, 50.9)
	M3	75.3 (56.9, 93.7)	50.9 (34.3, 67.5)	53.5 (35.5, 71.6)
IDSIQ total score	M1	-14.7 (-20.5, -8.9)	-9.6 (-14.8, -4.4)	-9.7 (-15.2, -4.1)
	M3	-21.9 (-29.3, -14.5)	-14.4 (-21.0, -7.7)	-17.8 (-25.1, -10.6)

Safety (Table 3)

- Two serious adverse events and two TEAEs leading to treatment discontinuation were reported, all within the placebo group.
- TEAEs related to somnolence were low and comparable across all groups.
- Morning sleepiness (VAS) improved in all treatment groups from baseline to M1 and M3.

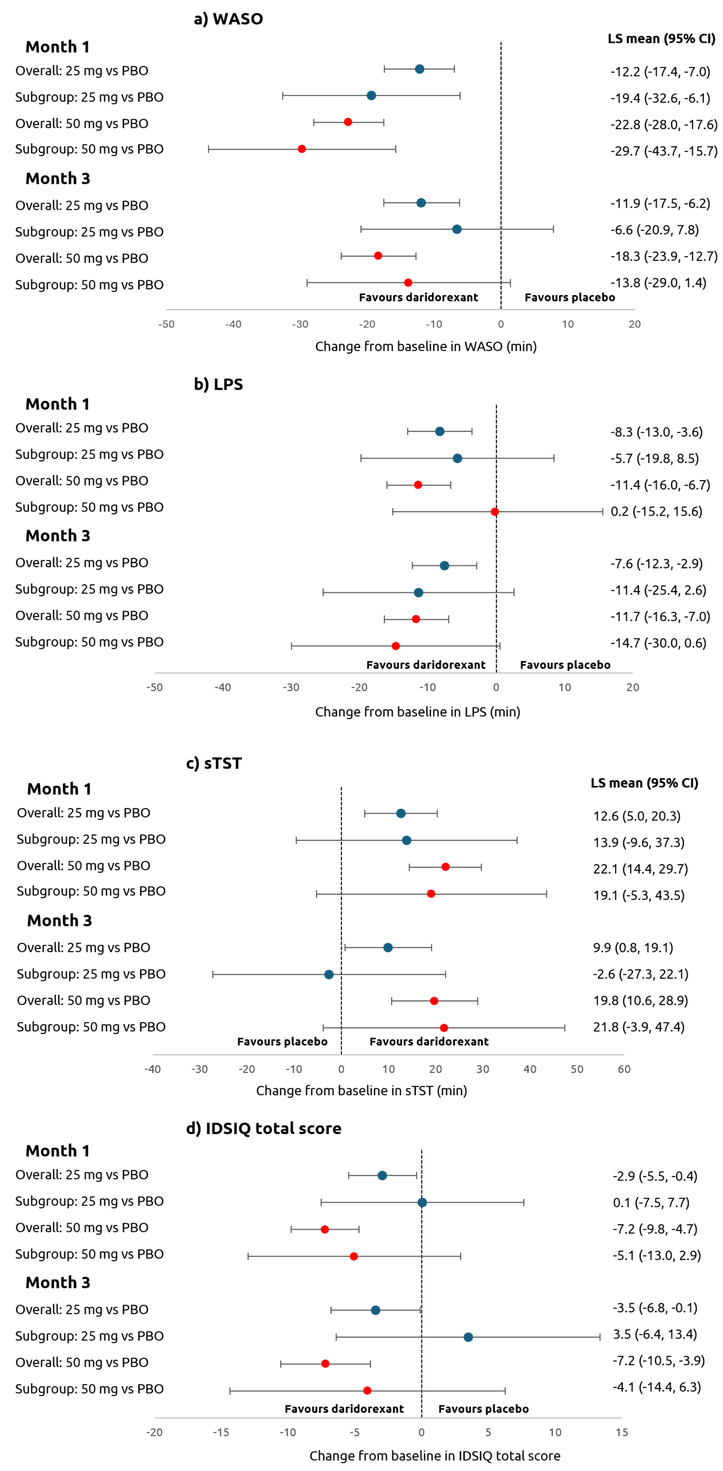
Table 3. Summary of adverse events

N (%)	Daridorexant 50 mg (n=35)	Daridorexant 25 mg (n=43)	Placebo (n=39)
Patients with ≥1 TEAE[a]	16 (46%)	15 (35%)	15 (38%)
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
Back pain	2 (6%)	0	0
Influenza	2 (6%)	0	0
Somnolence	1 (3%)	2 (5%)	3 (8%)
VAS morning sleepiness, mm, mean (SD)			
Change from baseline to M1	9.7 (14.2)	8.4 (13.3)	6.7 (13.8)
Change from baseline to M3	14.1 (18.5)	14.8 (19.3)	15.7 (20.6)

Includes all TEAEs in the double-blind study period up to 30 days after double-blind study treatment end date (or date of enrolment into extension study).

The VAS score ranges from 0 'very sleepy' to 100 'not sleepy at all'. A higher score indicates less morning sleepiness.

Figure 1. Nighttime & daytime efficacy: Placebo-corrected LSM change from baseline in sleep parameters and IDSIQ total score at M1 and M3



Conclusions

- **This subgroup post hoc analysis is the first evaluation of the efficacy and safety of daridorexant in women with insomnia disorder during the menopausal transition age.**
- **The data suggest that daridorexant 50 mg may provide a benefit in improving sleep onset, sleep maintenance and daytime functioning in this subgroup of women. Daridorexant was well tolerated, with no increased risk of next-morning sleepiness or daytime somnolence.**

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Disclosures

The study was funded by Idorsia Pharmaceuticals Ltd.

Z Schaedel has received speaker & advisory fees from Theramex, Besins, Idorsia, Astellas & Bayer. C Bassetti has served as consultant for Idorsia. P Cassel has received honoraria and travel expenses from Idorsia, Dr. Pfleger Arzneimittel GmbH & Mementor Deutschland GmbH. C Palmay has received honoraria from Abbvie, Allergan, Aspen, AZ, Bayer, Bausch Health, Galderma, GSK, Idorsia, Lundbeck, Lupin, Merck, Moderna, Novartis, Nuvopharm, Pfizer, Sanofi, Searchlight, Seqirus, Sunovion, Sunpharma, & Valeant; consulting fees from Dr. Ho Medical, MDBriefcase, The Rounds, Eisai, Sunovion, CCRN. PeerVoice, CCRN Board Director, CTC, Abbvie. R Silverstri has received honoraria from Idorsia. F Trémollieres has received expert and/or conference fees from Astellas, Bayer, Besins Healthcare France & Theramex. SM Bertisch has received consulting fees from Idorsia & Elemind. S Palacios & P Stute have nothing to disclose. T Bakker, O Briasoulis & S Pain are employees of Idorsia Pharmaceuticals Ltd.

Poster presented at World Sleep 2025. Poster originally presented at the Congress of the European Academy of Neurology 2025.