

Effect of daridorexant on wakefulness throughout the night and morning sleepiness in patients with insomnia disorder

Yves Dauvilliers¹, Gary Zammit², Pierre-Philippe Luyet³, Guy Braunstein³, Antonio Olivieri³

¹Centre Hospitalier Universitaire de Montpellier, Montpellier, France; ²Clinilabs Drug Development Corporation, New York, United States; ³Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland

Introduction

- Reducing wakefulness throughout the entire night without residual effects the next morning (e.g. sleepiness) are essential characteristics for drugs for chronic insomnia.¹
- Daridorexant is a dual orexin receptor antagonist approved for the treatment of chronic insomnia at two dose levels, 25 mg and 50 mg.²
- In Phase 3 trials, at Months 1 and 3 of treatment³:
 - Daridorexant significantly reduced polysomnography (PSG)-determined wake after sleep onset (WASO); no analysis was reported on the effect of daridorexant and placebo by quarter of the night.
 - Visual analogue scale (VAS) scores for morning sleepiness, daytime alertness and ability to function were not statistically tested but showed numerical dose-related improvements.

Study objective

- To examine the effect of daridorexant on WASO in each quarter of the night, the self-reported morning and daytime effect over the 3 months treatment period and the correlation between these night and daytime endpoints in patients with chronic insomnia.

Methods

Data set

- Data from a Phase 3, randomized, double-blind, placebo-controlled study of 930 patients evaluating daridorexant 50 mg (n=310) and 25 mg (n=310) compared to placebo (n=310) for 3 months in patients with chronic insomnia disorder (ClinicalTrials.gov identifier NCT03545191).³

WASO by quarter of the night analyses

- Eight-hour PSG assessments were performed on two consecutive nights during a single-blind placebo run-in period (baseline) and the double-blind treatment period at Month 1 and 3.
- WASO was defined as the total cumulative time (minutes) spent awake after onset of persistent sleep until lights on.
- WASO in each quarter of the night (i.e. each 2-hr period of the 8 hours PSG recording; Q1, Q2, Q3, and Q4) was extracted and the mean WASO of the two PSG nights at each timepoint analyzed.
- Change from baseline was analyzed using a linear mixed effects model for repeated measures.

Morning and daytime symptoms

- Participants completed a daily sleep diary throughout the study; this included a morning VAS assessing morning sleepiness, and two evening VAS assessing daytime alertness and ability to function.
- Change from baseline (weekly mean) was analyzed using a linear mixed effects model for repeated measures.

Correlations between nighttime and daytime measures

- Associations between WASO by quarter of the night and each VAS variable were assessed by calculating a single coefficient of correlation considering the repeated measures at Month 1 and Month 3 using a random-effects model based on bivariate normal distribution approach.
- Correlational analyses were based on the VAS values reported the morning or evening after the two PSG recordings at each timepoint.

Results

WASO by quarter of the night

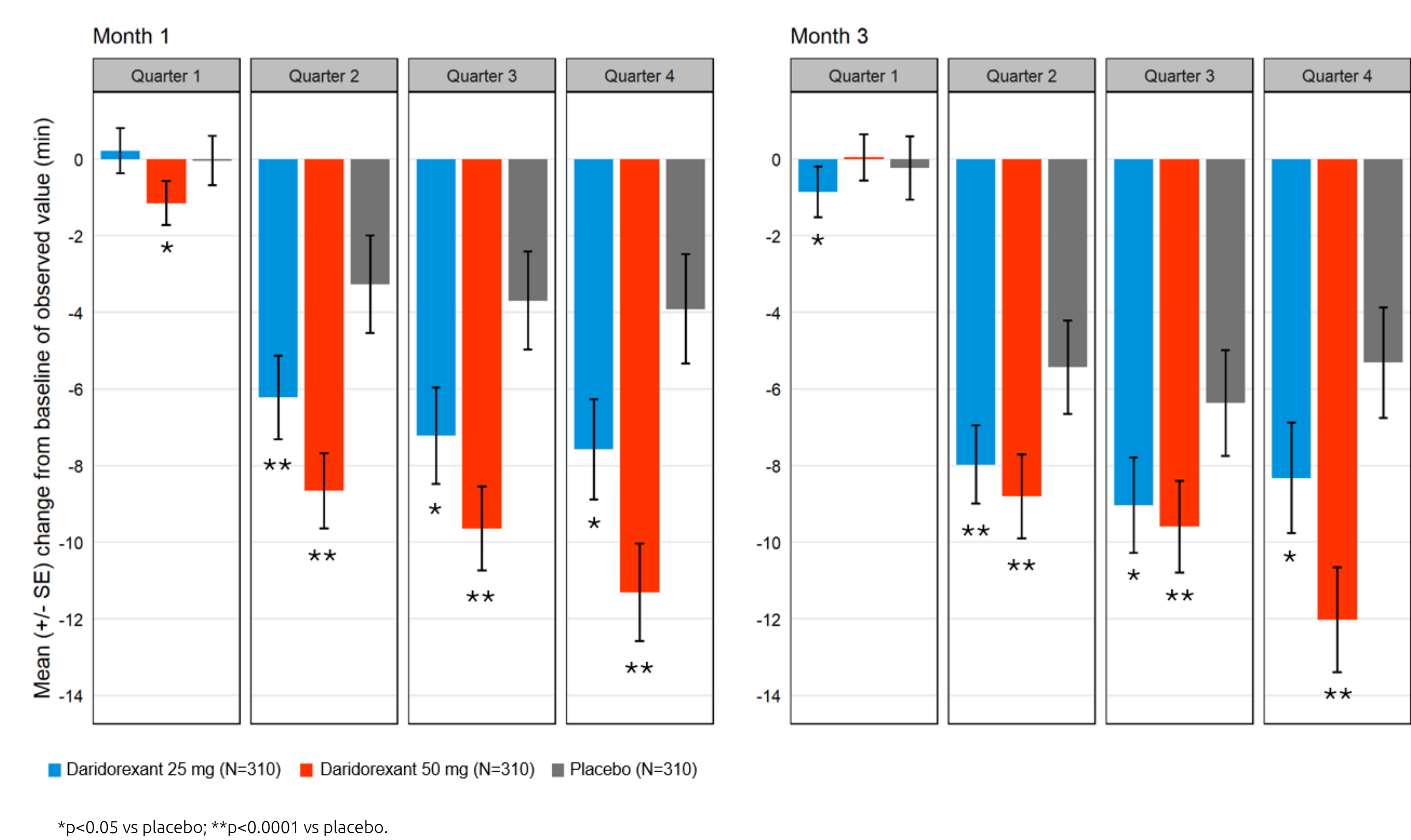
- At baseline, total mean WASO was 98.6 min.
- WASO increased progressively over the four quarters of the night. With a mean baseline latency to persistent sleep of 65.8 mins (~1 h), Q1 contributed modestly to the overall baseline WASO (9%) vs. Q2 (26%), Q3 (27%) and Q4 (39%) (Table 1).

Table 1. Summary of key PSG sleep parameters at baseline

Mean (SD)	All patients N=930
Wake after sleep onset, overall, min	98.6 (39.2)
Quarter 1, min	9.0 (9.4)
Quarter 2, min	24.8 (18.4)
Quarter 3, min	27.2 (18.8)
Quarter 4, min	38.9 (23.4)
Latency to persistent sleep, min	65.8 (38.6)
Total sleep time, min	323.1 (53.4)

- Daridorexant 25 mg and 50 mg significantly decreased WASO from baseline in Q2, Q3 and Q4 versus placebo at Month 1 and 3 (Figure 1).
- The reductions in each quarter increased progressively over the night, in particular for daridorexant 50 mg.
- Reductions in WASO in each quarter were consistently greater in the daridorexant 50 mg group compared to 25 mg.

Figure 1. Mean change from baseline in WASO (in min) by quarter of the night at Months 1 and 3



*p<0.05 vs placebo; **p<0.0001 vs placebo.

Morning and daytime symptoms

- Daily VAS scores for morning sleepiness, daytime alertness and ability to function progressively increased (i.e. improved) in a dose-dependent manner from baseline up to the end of treatment with both doses of daridorexant versus placebo from as early as Day 1.
- Treatment was numerically ranked as daridorexant 50 mg > 25 mg > placebo.
- For all three VAS scores, the treatment effect of daridorexant 50 mg versus placebo was statistically significant at every weekly time point from Week 2 onwards (Figure 2).

Correlation between the nighttime and daytime measures

- Strong positive correlations were found between the self-reported VAS scores (Figure 3).
- No clinically important correlations between WASO for each quarter of the night and any of the VAS scores.

Figure 2. Weekly change from baseline in morning sleepiness, daytime alertness and daytime ability to function

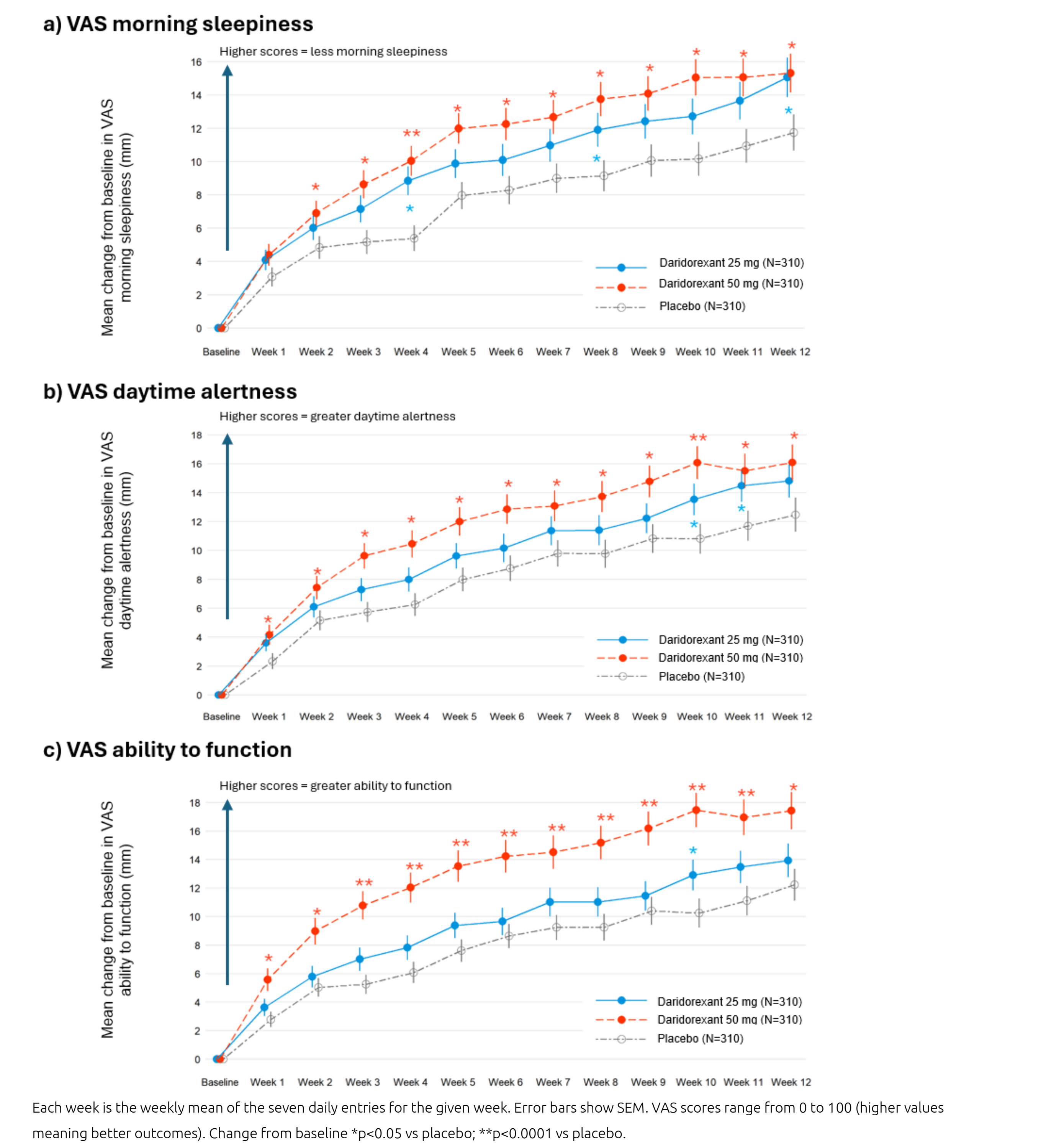
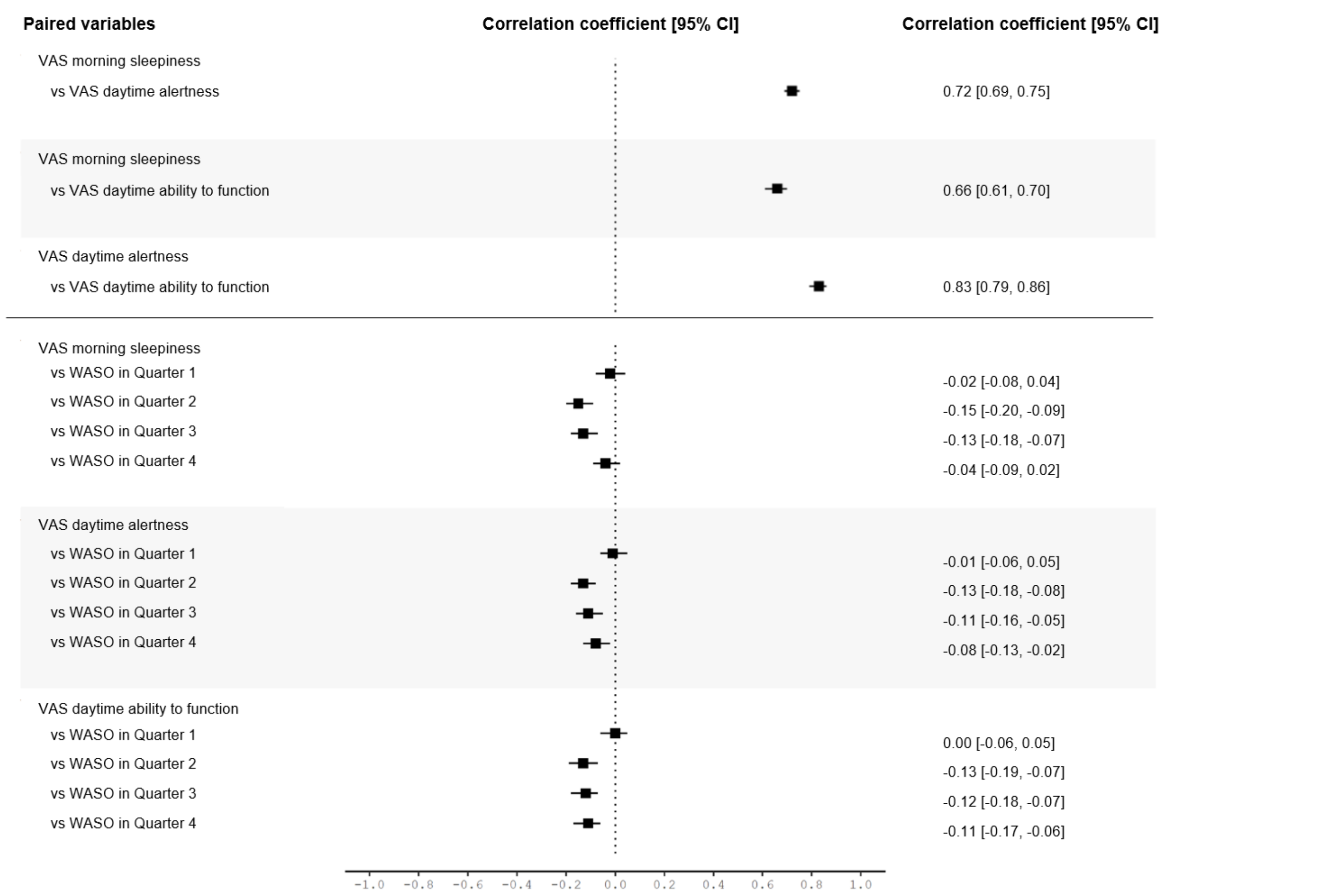


Figure 3. Coefficients of correlation between change from baseline in VAS parameters and between change from baseline in WASO by quarter of the night and VAS parameters



References

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- Markham, A. Drugs. 2002; 82: 601-607.
- Mignot E, et al. Lancet Neurol. 2022;21:125-139.

Disclosures

The study was funded by Idorsia Pharmaceuticals Ltd. YD reports board membership, consultancy, and lecture activity with Idorsia. GZ is an employee of Clinilabs Drug Development Corporation, a company that has received grants from Idorsia and reports consultancy activity with Idorsia. AO, GB and PPL are employees of Idorsia Pharmaceuticals Ltd. .

Conclusions

- In patients with chronic insomnia, daridorexant significantly reduces wakefulness (WASO) throughout the night, including the last two hours, while independently decreasing morning sleepiness and improving daytime ability to function and alertness, with a larger and more consistent effect with daridorexant 50 mg.
- Given the unmet need for drugs that promote sleep maintenance for the entire night without inducing next-day sedation, these findings are of much clinical relevance.