

Efficacy and Safety of Daridorexant in Individuals with Insomnia with Short Sleep Duration

Julio Fernandez-Mendoza¹, Paul Saskin², Joana Marques Barros³, Fjola Sigurdarottadir⁴, Yves Dauvilliers⁵

¹Penn State University-Hershey, PA, USA; ²Idorsia Pharmaceuticals US, Radnor PA, USA; ³Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland;

⁴University of Oslo, Norway; ⁵Guy De Chauillac Hospital, Montpellier, France

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Introduction

- Insomnia with short sleep duration has been identified as a distinctive more severe phenotype, notable for increased physiological hyperarousal and cardiometabolic risk¹ with an associated blunted response to cognitive behavioral therapy for insomnia
- Daridorexant, a dual orexin receptor antagonist, has demonstrated efficacy and safety in individuals with insomnia disorder in a large clinical trial (NCT03545191)

Study objective

To examine the efficacy and safety of daridorexant 50 mg in insomnia disorder with PSG-determined short sleep duration (<330 minutes)

Methods

- Post-hoc analysis of clinical trial NCT03545191, the details of which are described elsewhere². Briefly, participants with insomnia disorder were randomized (1:1:1) to daridorexant 25mg, 50mg or placebo for 12 weeks
- Inclusion criteria: Latency to Persistent Sleep (LPS) of ≥ 20 minutes and an objective Total Sleep Time (TST) of <420 minutes on average, on 2 consecutive nights of attended polysomnography
- The median objective TST of 330 minutes was used to divide the subjects into two groups (Table 1). This threshold differs from the 360 mins in the abstract and was used given that the inclusion/exclusion criteria for the study resulted in a distribution of objective TST that was different than observed in population-based samples. The exclusion criterion of <420 minutes TST on baseline assessment resulted in a ceiling effect that limited the number of individuals with objective TST >360 minutes. Subjects with insomnia and “short” sleep duration (<330 minutes) slept an average of 4.7 hours (0.7 hours), while those with insomnia and “normative” sleep duration (≥ 330 minutes) slept on average for 6.1 (0.4) hours
- In this post-hoc analysis, the effects of the 50 mg dose vs placebo will be presented:
 - Objective endpoints: Change from baseline in PSG-measured Wake After Sleep onset (WASO), LPS, and TST at months 1 & 3
 - Subjective endpoints: Change in eDiary-measured subjective TST and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) Sleepiness Domain score at months 1 & 3

Results

Table 1. Baseline clinical characteristics

	Total	50 mg	Placebo
<330 min	460	135	170
Age mean (SD)	57.5 (14.7)	57.5 (15.4)	57.1 (14.9)
Female	64%	59%	64%
BMI mean (SD)	26.8 (4.3)	26.5 (4.5)	26.6 (4.0)
ISI mean (SD)	19.3 (4.1)	19.4 (3.9)	19.6 (3.9)
TST mean (SD)	281.8 (42.6)	284.3 (41.3)	281.0 (41.7)
≥ 330 min	468	174	139
Age mean (SD)	53.4 (15.7)	53.8 (15.1)	52.6 (15.7)
Female	71%	68%	73%
BMI mean (SD)	26.2 (4.2)	26.1 (4.2)	26.2 (4.2)
ISI mean (SD)	19.0 (4.1)	19.2 (4.1)	18.6 (4.2)
TST mean (SD)	363.7 (23.3)	362.3 (22.1)	364.7 (24.6)

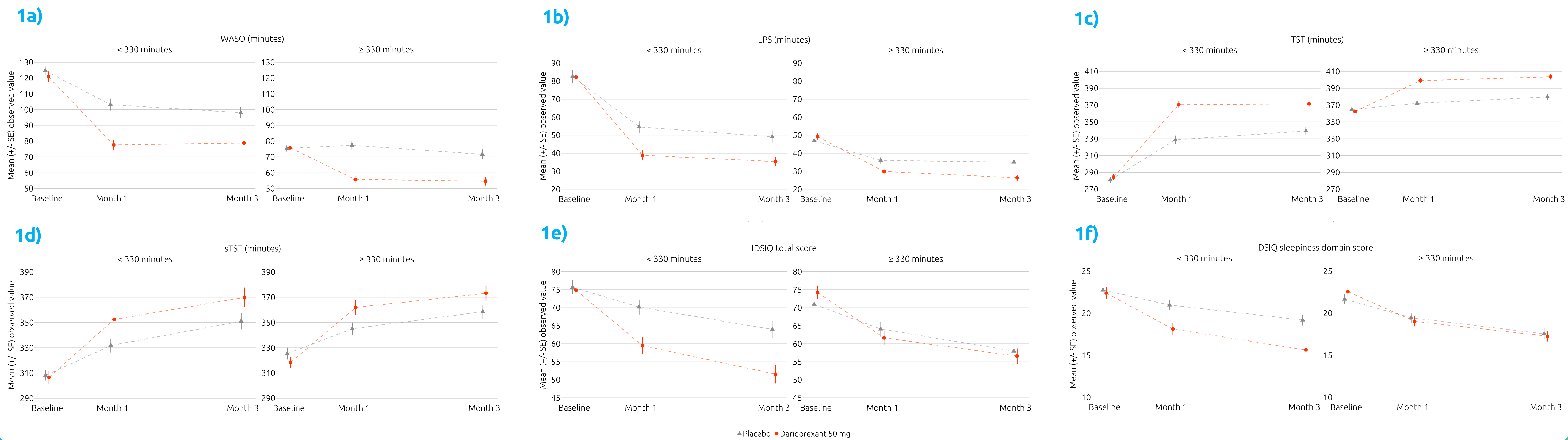
Table 2. Safety features of daridorexant were similar for both groups and consistent with placebo.

	<330 min	Daridorexant 50 mg N=135	Placebo N=170
Patients with ≥ 1 TEAE		52 (38.5%)	60 (35.3%)
TEAE ≥ 2 patients in any group:			
Nasopharyngitis		9 (6.7%)	11 (6.5%)
Headache		9 (6.7%)	7 (4.1%)
Somnolence		0	2 (1.2%)
Fatigue		4 (3.0%)	0
Dizziness		2 (1.5%)	1 (0.6%)
Depressed Mood		0	0
Falls		1 (0.7%)	6 (3.5%)
Abnormal Dreams		0	1 (0.6%)

	≥ 330 min	Daridorexant 50 mg N=173	Placebo N=138
Patients with ≥ 1 TEAE		69 (39.9%)	54 (39.1%)
TEAE ≥ 2 patients in any group:			
Nasopharyngitis		15 (8.7%)	12 (8.7%)
Headache		11 (6.4%)	5 (3.6%)
Somnolence		6 (3.5%)	5 (3.6%)
Fatigue		4 (2.3%)	2 (1.4%)
Dizziness		5 (2.9%)	1 (0.7%)
Depressed Mood		1 (0.6%)	0
Falls		0	2 (1.4%)
Abnormal Dreams		0	1 (0.7%)

Figure 1. Objective and subjective measures of sleep and daytime functioning

- Subjects with short sleep showed improvement on all measures of sleep - Figs 1a (WASO), 1b (LPS), 1c (TST), 1d (subjective TST)
- Improvement in daytime functioning was shown both for the sleepiness domain and for the total score, indicative of better mood, cognition and alertness - Figs 1e (IDSIQ Total), Fig 1f (IDSIQ Sleepiness)
- While most of the improvements in objective parameters were observed by month 1 and maintained at month 3, improvements in sTST and daytime functioning continued throughout the 3-month treatment period
- Similar results were observed in the ≥ 330 minute subgroup



References

- Vgontzas AN et al. Sleep. 2009;32:491–497
- Mignot E et al. Lancet Neurology, 2022, 21: 125-139.

Disclosures

The study was funded by Idorsia Pharmaceuticals Ltd. PS, and JMB are current employees of Idorsia Pharmaceuticals. YD is a scientific advisor to Idorsia Pharmaceuticals. JFM and FS have no conflicts to report

Conclusions

In subjects with insomnia disorder and short-sleep duration, improvements in objective sleep parameters, subjective sleep duration, and daytime functioning were observed with daridorexant 50 mg nightly versus placebo.

The continued safety profile of daridorexant 50 mg, with findings generally consistent with placebo, adds to the overall evidence supporting its use in patients with insomnia disorder, including those with the severe short-sleep phenotype.

