Effect of daridorexant on wakefulness throughout the night: Post hoc analysis of a randomised, double-blind, active reference (zolpidem) study in patients with insomnia disorder

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Background

- Reducing wakefulness throughout the entire night is a key goal for the treatment of insomnia disorder
- Daridorexant, a dual orexin receptor antagonist, is approved at doses of 25 mg and 50 mg for the treatment of insomnia disorder in adults in the US, EU, UK, Switzerland, Canada, Hong-Kong, and Japan
- Daridorexant selectively reduces the orexin-induced wake signaling[1]
- Daridorexant induces significant dose-dependent reductions in wake time after sleep onset (WASO) and in latency to persistent sleep, and improvements in subjective total sleep time, and Insomnia Daytime Symptoms and Impacts Questionnaire total score[2,3]

Study objective

- Evaluate the dose-response effect of daridorexant (5, 10, 25, and 50 mg) on polysomnography (PSG)-determined WASO throughout the night (by quarter of the night [QoN]) compared with placebo and the GABA-receptor agonist zolpidem, which induces sleep through widespread CNS sedation

Methods

- Post hoc analysis of the double-blind, randomized, placebo-controlled, parallel-group, dose-response Phase 2 study assessing the efficacy and safety of daridorexant in adults (18–64 years) with insomnia disorder (NCT02839200)
- Participants were randomized (1:1:1:1:1:1) to placebo, daridorexant (5, 10, 25, or 50mg), or zolpidem (10mg)
- WASO was assessed using descriptive statistics by QoN (Q1–Q4), i.e. every 2 hours over 8 hours at Days 1&2 (primary endpoint), 15&16, and 28&29
- Baseline values were derived from the two PSG nights during run-in, and Days 1&2 values from the first two PSG treatment nights; Days 15&16 and 28&29 were defined similarly

Results

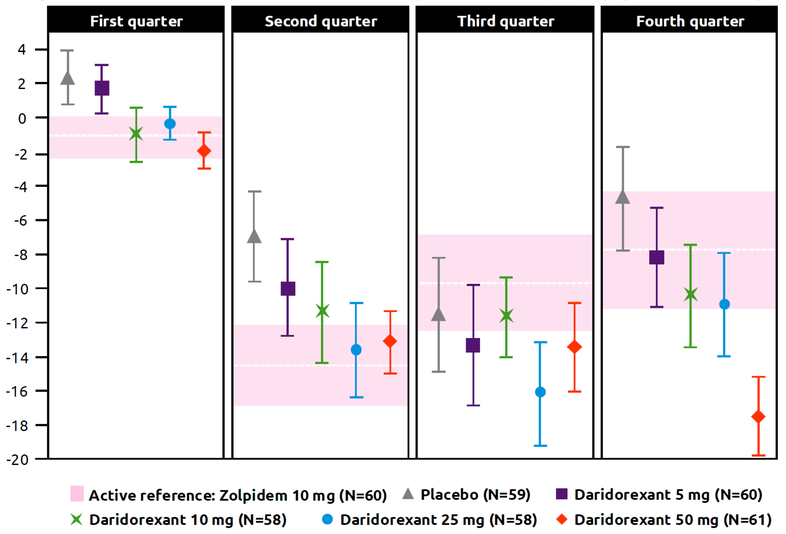
- A total of 359 subjects were enrolled in the study
- The majority of subjects were female (64.1%), and White (89.4%) with a mean age at screening of 44.7 years, and a mean body mass index (± SD) of 25.2 ± 3.3 kg/m^2
- The treatment groups were generally well balanced (Table 1)
- Mean WASO was reduced at Days 1&2 for all treatment groups: −20.98 min (placebo), −28.99 min, −33.75 min, −39.64 min, and −45.49 min (daridorexant doses of 5, 10, 25, and 50 mg), and −31.23 min (zolpidem).
- Dose-dependent decreases in mean WASO by QoN from baseline to Days 1&2 are shown in Figure 1
- During Q1 and Q2 the approved doses of daridorexant provided a similar response compared with zolpidem 10mg (Figure 1)
- During Q3, mean reductions in WASO were numerically greater with daridorexant 25 mg and 50 mg versus zolpidem 10 mg (–16.15 min and –13.49 min versus –9.73 min, respectively)
- During Q4, mean reductions in WASO were numerically greater with daridorexant 50 mg (–17.51 min) versus zolpidem 10 mg (–7.81 min); daridorexant 50 mg had the most pronounced effect on WASO compared with other QoN
- Similar effects were observed at Days 15&16, and Days 28&29 (not shown)

Table 1: Baseline demographics and disease parameters

	Daridorexant 5mg (N=60)	Daridorexant 10 mg (N=58)	Daridorexant 25 mg (N=60)	Daridorexant 50 mg (N=61)	Placebo (N=60)	Zolpidem 10 mg (N=60)
Age, years, mean (SD)	42.4 (11.4)	45.2 (10.9)	46.4 (11.9)	45.0 (11.5)	45.7 (10.4)	43.7 (11.8)
Female Sex, n (%)	38 (63.3)	38 (65.5)	39 (65.0)	39 (63.9)	38 (63.3)	38 (63.3)
Race, n (%)						
Asian	0	0	0	0	1 (1.7)	0
Black or African American	5 (8.3)	8 (13.8)	4 (6.7)	5 (8.2)	7 (11.7)	6 (10.0)
White	54 (90.0)	49 (84.5)	56 (93.3)	56 (91.8)	52 (86.7)	54 (90.0)
Other*	1 (1.7)	1 (1.7)	0	0	0	0
BMI, kg/m^2, mean (SD)	24.9 (3.2)	25.4 (3.4)	24.9 (3.3)	24.5 (2.9)	25.4 (3.3)	26.0 (3.5)
WASO, min, mean (SD)	97.4 (47.1)	98.8 (36.3)	99.6 (40.9)	94.0 (31.9)	95.8 (34.7)	99.2 (38.8)
LPS, min, mean (SD)	72.7 (51.9)	66.1 (31.8)	74.3 (43.5)	69.6 (30.2)	74.3 (39.3)	73.4 (34.8)
TST, mean (SD), min	317.8 (73.6)	322.4 (50.4)	313.7 (57.1)	323.3 (45.6)	317.7 (53.9)	315.8 (54.9)

*Includes Native Hawaiian or other Pacific Islander; other
BMI, body-mass index; LPS, latency to persistent sleep; SD, standard deviation; TST, total sleep time; WASO, wake time after sleep onset

Figure 1: Mean ± SE change from baseline to Days1&2 in WASO (min) by quarter of the night



Conclusions

- In patients with insomnia disorder, daridorexant reduces wakefulness in a dose-dependent manner throughout the entire night
- A key symptom of insomnia disorder is early awakening with an inability to return to sleep.[4,5] Our results suggest that daridorexant, particularly at the dose of 50 mg, alleviates this manifestation and facilitates sleep to occur until the end of the night
- The effects of daridorexant on wakefulness are observed in the first night after treatment and are maintained throughout the study (30 days)
- In the second half of the night, daridorexant 50 mg shows a numerically greater reduction in WASO compared with zolpidem 10 mg

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