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Original Article

Assessment of the effect of the dual orexin receptor antagonist daridorexant on various indices of disease severity in patients with mild to moderate obstructive sleep apnea



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ABSTRACT

Background: The dual orexin receptor antagonist daridorexant did not impact nighttime respiratory function as assessed by the apnea/hypopnea index (AHI) and nocturnal oxygen saturation (SpO_2) and improved sleep in patients with mild to moderate obstructive sleep apnea (OSA). These analyses were supplemented with further evaluations of various indices of OSA severity and sleep variables.

Methods: In this randomized, double-blind, placebo-controlled, two-period, crossover study, 50 mg daridorexant or placebo was administered every evening for 5 days to 28 patients with mild to moderate OSA. Treatment differences (daridorexant – placebo) were explored for indices of OSA severity including the number and duration of apneas and hypopneas, mean and lowest nocturnal SpO_2 , sleep duration during each hour of polysomnography recording, and the number and mean and longest duration of awakenings.

Results: After repeated-dose daridorexant, more respiratory events were observed compared to placebo, ie., treatment difference of 16.4 events (90% confidence interval: -0.4, 33.2) which is explained by a longer total sleep time. However, no treatment difference was detected for the longest duration of apneas and hypopneas (1.5 s [-8.3, 11.2] and 8.2 s [-6.6, 23.0], respectively), and lowest SpO_2 (0.9% [-0.3, 2.1]). The number of awakenings was similar between daridorexant and placebo while daridorexant shortened the longest duration by 16.2 min (8.5, 23.8).

Overall, results were similar after single and repeated dosing for both respiratory and sleep aspects.

Conclusion: These results suggest safe use of daridorexant in patients with mild to moderate OSA.

Clinical trial registration: ClinicalTrials.gov NCT03765294. A study to investigate the effects of ACT-541468 on nighttime respiratory function in patients with mild to moderate obstructive sleep apnea. <https://clinicaltrials.gov/ct2/show/NCT03765294>.

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1. Introduction

Obstructive sleep apnea (OSA) is a breathing disorder characterized by repeated reduction (ie, hypopnea) or cessation (ie, apnea) of breathing during sleep due to the temporary collapse of the upper airway [1,2]. It is known to increase daytime sleepiness [3], to

impair quality of life [4]), and to increase the burden of cardiovascular diseases [2,5,6] or type 2 diabetes [7,8].

OSA coexists with insomnia in up to 30% of patients [9,10] but remains largely undiagnosed [11].

Dual orexin receptor antagonists (DORAs) have evolved as a new pharmaceutical class for treatment of insomnia [12]. Orexin neuropeptides A and B promote alertness/wakefulness by interacting with both the orexin-1 and orexin-2 receptors [13].

Two DORAs, suvorexant and lemborexant, have been approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance [14,15].

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Daridorexant (ACT-541468) is a new DORA that reduces overactive wake signaling, with appropriate pharmacokinetic and pharmacodynamic properties to improve both sleep and daytime functioning [12,16,17].

Daridorexant has recently been shown not to have a clinically meaningful effect on apnea/hypopnea index (AHI) and nighttime peripheral oxygen saturation (SpO_2) at the highest Phase 3 dose of 50 mg in patients with mild and moderate OSA [18].

Although AHI and mean SpO_2 during total sleep time (TST) are used for the diagnosis of OSA [19] and in safety respiratory studies [20], they might not cover the full spectrum of nighttime respiratory safety in patients with OSA [21]. Other aspects including, but not limited to, the number and duration of apneas and hypopneas and lowest SpO_2 during these respiratory events are relevant to claim safe use of sleep-promoting agents in patients with OSA.

In order to evaluate the influence of daridorexant on nighttime respiratory variables beyond AHI and SpO_2 during TST, additional post-hoc analyses were performed from the initial study [18]. Here we report the first comprehensive evaluation of a DORA on a spectrum of respiratory and sleep variables.

2. Methods

2.1. Study design

This randomized, double-blind, placebo-controlled, 2-period crossover study aimed to investigate the effects of daridorexant on nighttime respiration-related variables and sleep characteristics in male and female patients with mild (ie., AHI from 5 to < 15 events/h) and moderate OSA (ie., AHI from 15 to < 30 events/h) [22,23]. The study protocol was approved by the German health authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) and by the local Ethics committee (Ethik-Kommission des Landes Berlin, Berlin, Germany). The study was conducted at a single study site (ASR Berlin, Germany) in accordance with the Declaration of Helsinki principles, International Council for Harmonisation, Good Clinical Practice guidelines, and applicable regulations and laws. Each patient provided written informed consent prior to any screening procedures.

The study design has previously been described [18]. Briefly, 28 patients were randomized in a 1:1 ratio to receive evening, oral doses of daridorexant (50 mg once daily) followed by matching placebo or vice versa for 5 days with a 1- to 2-week washout period.

To be enrolled in the study, absence of respiratory disorders other than OSA or any other disease with a potential impact on sleep, motor performance, or cognition (ie., psychiatric disease including suicidal ideation, neurological disorder, or severe insomnia) was required. Former and current use of continuous positive airway pressure (CPAP) or dental appliance devices was prohibited.

Standard 8 h polysomnography (PSG) recordings and SpO_2 measurements were performed at screening as well as after first (Night 1) and last dosing (Night 5) using MiniScreen PRO v5.19.0 (Löwenstein Medical, Rheinland-Pfalz, Germany). In both study periods, first and last dosing occurred at study site, while study treatments were self-administered at home from Night 2 to Night 4. Study staff contacted the patients each day to ensure adherence to treatment intake.

2.2. Respiratory and sleep variables

Primary study results based on AHI and SpO_2 have previously been reported [18].

The effect of daridorexant was further analyzed with respect to the following variables:

- (i) indices of OSA severity: number as well as mean and longest duration of apneas and hypopneas per nighttime sleep phase (ie., TST, rapid eye movement [REM], and non-REM) and stage (ie., N1, N2, and N3) as well as mean SpO_2 during sleep stages N1, N2, and N3, time spent with $\text{SpO}_2 < 90\%$, <85%, and <80% during non-REM and REM sleep, and mean and lowest SpO_2 during respiratory events. An apnea was defined as a pause of respiration for at least 10 s, while a hypopnea was defined as a reduction of airflow by at least 30% for at least 10 s accompanied by an absolute decrease of SpO_2 by ≥ 3% (ie., 3 units) compared to corresponding data prior to the hypopnea event and/or the event was associated with an arousal.
- (ii) sleep duration during each h of PSG recording as well as number, mean, and longest duration of awakenings. An awakening was defined as time spent awake for at least 15 s and scored in a 30 s window (ie., epoch).

Each variable was evaluated after first and last dosing of daridorexant and placebo. All variables were scored in a blinded manner according to the current AASM criteria [22].

2.3. Statistical analysis

Treatment differences (daridorexant – placebo) were evaluated by linear mixed-effect modeling, which included treatment, period, and baseline (ie., data from PSG performed at screening) as fixed effects, and subject as random effect. Mean square errors from the model were used to calculate the two-sided 90% confidence interval (CI) for the mean treatment differences (daridorexant – placebo) of each variable. Study results are reported as individual treatment differences (figures only) and least squares mean differences with two-sided 90% CI.

The least square approach was used for linear regression analysis of AHI during TST at baseline (ie., OSA severity) and treatment difference (daridorexant – placebo) for the number and longest duration of apneas + hypopneas, and the lowest SpO_2 during respiratory events.

Sample size was determined based on power analysis for the primary endpoint [18]. No type I error control was established for the present analyses and results are descriptive. A variable was considered as increased or decreased after daridorexant administration compared to placebo when the 90% CI of the treatment difference did not contain 0.

3. Results

3.1. Subject disposition

Out of the 28 enrolled patients, 25 were evaluable, while 3 were excluded from the analysis due to premature study discontinuation [18].

3.2. Influence of daridorexant on nighttime respiration-related variables

The influence of single and repeated dosing of daridorexant (50 mg) on nighttime respiration-related variables is provided in Table 1, and Figs. 1 and 2.

After single and repeated dosing of daridorexant, the total number of respiratory events (apneas + hypopneas) during TST was slightly higher compared to placebo, ie., a treatment difference of

Table 1

Influence of daridorexant on nighttime respiration-related variables.

	Single dosing (N = 25)			Repeated dosing for 5 days (N = 25) ^a		
	Daridorexant (50 mg)	Placebo	Treatment difference (daridorexant – placebo)	Daridorexant (50 mg)	Placebo	Treatment difference (daridorexant – placebo)
Number of apneas + hypopneas during						
TST	112 (98.3, 126)	96.1 (82.1, 110)	16.2 (−1.9, 34.3)	102 (88.5, 116)	86.2 (72.1, 100)	16.4 (−0.4, 33.2)
Non-REM	97.5 (84.6, 110)	79.1 (66.2, 92.0)	18.4 (0.6, 36.3)	84.3 (71.4, 97.1)	73.7 (60.9, 86.6)	10.5 (−5.3, 26.3)
N1	20.0 (15.8, 24.2)	14.9 (10.8, 19.1)	5.10 (−0.5, 10.6)	22.1 (17.9, 26.3)	18.6 (14.4, 22.9)	3.5 (−1.8, 8.8)
N2	68.6 (57.7, 79.5)	54.9 (44.0, 65.8)	13.7 (−0.1, 27.5)	55.1 (44.0, 66.2)	44.6 (33.5, 55.7)	10.5 (−4.2, 25.2)
N3	9.1 (3.2, 14.9)	9.2 (3.3, 15.0)	−0.1 (−7.0, 6.8)	7.2 (2.4, 12.0)	10.9 (6.1, 15.7)	−3.7 (−7.8, 0.3)
REM	13.3 (9.5, 17.1)	17.4 (13.6, 21.3)	−4.1 (−7.9, −0.3)	18.3 (13.6, 23.0)	13.4 (8.6, 18.2)	4.9 (−0.7, 10.5)
Number of apneas during TST	51.0 (39.9, 62.1)	30.9 (19.8, 42.0)	20.1 (4.6, 35.7)	37.4 (29.2, 45.6)	33.3 (25.1, 41.4)	4.1 (−4.7, 12.9)
Number of hypopneas during TST	61.3 (53.6, 69.0)	65.2 (57.5, 72.9)	−3.9 (−13.9, 6.0)	65.2 (53.7, 76.7)	53.0 (41.5, 64.5)	12.3 (−1.8, 26.3)
Duration of apneas [sec]						
Mean	32.8 (29.9, 35.8)	30.5 (27.6, 33.5)	2.3 (−1.7, 6.3)	30.4 (28.0, 32.9)	30.4 (28.0, 32.9)	0.0 (−2.6, 2.7)
Longest	46.1 (37.6, 54.6)	43.9 (35.4, 52.4)	2.1 (−8.8, 13.1)	50.8 (40.5, 61.1)	49.3 (39.0, 59.7)	1.5 (−8.3, 11.2)
Duration of hypopneas [sec]						
Mean	23.3 (20.9, 25.8)	21.5 (19.0, 23.9)	1.8 (−0.7, 4.4)	23.4 (20.5, 26.3)	23.4 (20.5, 26.2)	0.0 (−2.4, 2.5)
Longest	87.8 (71.2, 104)	86.6 (70.0, 103)	1.2 (−22.9, 25.3)	78.1 (66.3, 89.8)	69.8 (58.1, 81.6)	8.2 (−6.6, 23.0)
Mean SpO ₂ during [%]						
N1	93.7 (93.5, 94.0)	94.2 (93.9, 94.4)	−0.4 (−0.8, −0.1)	93.9 (93.6, 94.3)	93.7 (93.3, 94.1)	0.23 (−0.3, 0.6)
N2	93.6 (93.3, 93.9)	93.9 (93.6, 94.2)	−0.3 (−0.6, 0.0)	93.9 (93.5, 94.3)	93.6 (93.3, 94.0)	0.2 (−0.2, 0.6)
N3	93.7 (93.3, 94.1)	94.1 (93.7, 94.5)	−0.5 (−0.9, −0.0)	94.0 (93.5, 94.4)	93.8 (93.3, 94.2)	0.2 (−0.2, 0.6)
Non-REM with SpO ₂ [%non-REM]						
<90%	2.9 (2.1, 3.8)	1.6 (0.7, 2.5)	1.3 (0.3, 2.4)	1.6 (−1.7, 4.9)	5.3 (2.1, 8.6)	−3.7 (−8.1, 0.7)
<85%	0.2 (0.1, 0.3)	0.1 (0.0, 0.2)	0.1 (−0.0, 0.3)	0.3 (0.0, 0.3)	0.1 (−0.0, 0.3)	0.0 (−0.2, 0.3)
REM with SpO ₂ [%REM]						
<90%	3.1 (0.1, 6.0)	5.2 (2.3, 8.1)	−2.1 (−6.4, 2.2)	2.9 (0.1, 5.8)	4.9 (2.1, 7.8)	−2.0 (−5.3, 1.3)
<85%	0.4 (0.0, 0.9)	0.4 (0.0, 0.8)	0.0 (−0.7, 0.8)	0.2 (0.0, 0.4)	0.0 (0.0, 0.2)	0.2 (−0.2, 0.5)
SpO ₂ during respiratory events [%]						
Mean	90.6 (90.2, 91.0)	91.2 (90.8, 91.7)	−0.6 (−1.2, −0.1)	91.2 (90.7, 91.7)	90.9 (90.4, 91.4)	0.3 (−0.2, 0.7)
Lowest	81.0 (79.5, 82.4)	83.6 (82.1, 85.0)	−2.6 (−4.4, −0.8)	82.9 (81.4, 84.3)	82.0 (80.5, 83.4)	0.9 (−0.3, 2.1)

Data are displayed as least squares mean (95% CI) for treatments and (90% CI) for treatment difference.

Time spent with SpO₂ < 90% and <85% is expressed as %non-REM and %REM. To this end, the time spent in min with SpO₂ < 90% and <85% during non-REM and REM was divided by non-REM and REM duration, respectively.CI = confidence interval; REM = rapid eye movement; SpO₂ = peripheral oxygen saturation; TST = total sleep time.^a Study treatments were administered once daily in the evening.

16.2 events (90% CI: −1.9, 34.3) and 16.4 (90% CI: −0.4, 33.2; Fig. 1a), respectively. After repeated dosing of daridorexant, more apneas and hypopneas were observed compared to placebo (treatment difference of 4.1 [−4.7, 12.9] and 12.3 [−1.8, 26.3], respectively, while after single dosing, only the number of apneas was increased after daridorexant administration (treatment difference of 20.1 [4.6, 35.7]) vs hypopneas (−3.9 [−13.9, 6.0]). When evaluating the change of OSA severity category, 1 and 2 subjects on daridorexant and placebo, respectively, moved from mild to moderate, 3 and 2 subjects from moderate to severe, 7 and 6 subjects from moderate to mild, and 15 and 14 subjects remained unchanged.

AHI at baseline as a marker of OSA severity did not correlate with the treatment differences for the number of respiratory events after single ($r^2 = 0.010$; $p = 0.63$) and repeated dosing ($r^2 = 0.005$; $p = 0.73$; Fig. 2a).

More respiratory events were observed in both non-REM and REM sleep after repeated dosing of daridorexant compared to placebo (Table 1). However, after single dosing, the number of respiratory events was increased during non-REM sleep and decreased during REM sleep, ie., treatment difference of 18.4 (90% CI: 0.6, 36.3) and −4.1 (90% CI: −7.9, −0.3), respectively. Further analysis for each of the non-REM sleep stages revealed that the number of apneas + hypopneas was decreased during N3 but slightly increased during N1 and N2 after repeated dosing of daridorexant compared to placebo (Table 1). After single dosing, results were similar except for N3 during which a comparable number of respiratory events was observed after daridorexant administration compared to placebo.

Mean and longest duration of apneas and hypopneas were comparable between daridorexant and placebo after single and

repeated dosing (Table 1, Fig. 1b). AHI at baseline did not correlate with the treatment difference for longest duration of apneas and hypopneas after single ($r^2 = 0.029$; $p = 0.23$) and repeated dosing ($r^2 = 0.033$; $p = 0.21$; Fig. 2b).

After repeated dosing of daridorexant, time spent with SpO₂ < 90% or <85% during non-REM and REM sleep was similar to placebo (Table 1, Fig. 1c). This was also applicable for single dosing except for an increased time spent with SpO₂ < 90% during non-REM sleep, ie., treatment difference of 1.3% of non-REM (90% CI: 0.3, 2.4) (Table 1). As there were only 5 patients with SpO₂ < 80% during non-REM or REM sleep, the treatment difference for the time spent with SpO₂ < 80% was not evaluated. Four out of 5 subjects presented SpO₂ < 80% during non-REM sleep: 3 after daridorexant administration (2 after single [0.3% and 1.4% of non-REM sleep] and 1 after repeated dosing [2.7%]) and one after repeated dosing of placebo [0.4% of non-REM sleep]. One subject presented SpO₂ < 80% during REM sleep [2.7% of REM sleep] after single dosing of daridorexant.

After repeated dosing of daridorexant, mean SpO₂ was comparable to placebo during N1 to N3 sleep stages while after single dosing, mean SpO₂ was slightly decreased compared to placebo (Table 1).

Lowest SpO₂ during respiratory events was comparable between daridorexant and placebo after repeated dosing, ie., treatment difference of 0.9% (90% CI: −0.3, 2.1; Table 1, Fig. 1d), while after single dosing of daridorexant, it was slightly decreased compared to placebo, ie., treatment difference of −2.6% (90% CI: −4.4, −0.8) (Table 1). AHI at baseline did not correlate with the treatment differences for this endpoint after single ($r^2 = < 0.001$; $p = 0.99$) and repeated dosing ($r^2 = 0.091$; $p = 0.14$; Fig. 2c).

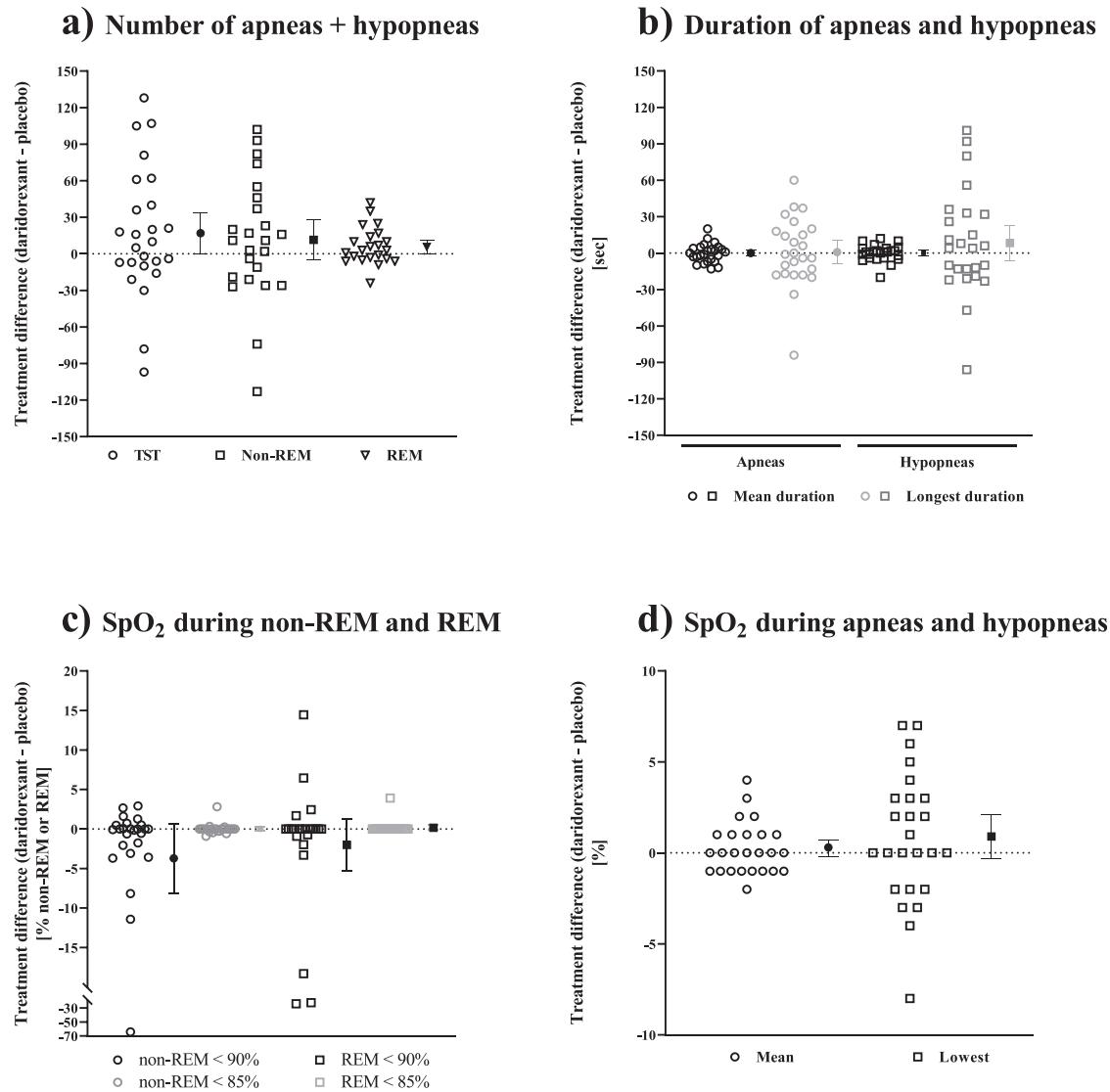


Fig. 1. Individual and mean ($\pm 90\%$ CI) treatment differences for respiration-related variables after repeated dosing ($N = 25$). Data are provided as individual (empty circles/squares/triangles) and least square means (90% CI; filled circles/squares/triangles) for treatment difference (daridorexant – placebo) after repeated dosing (Night 5). The panels refer to a) number of apneas + hypopneas, b) mean and longest duration of apneas and hypopneas, c) time spent with $\text{SpO}_2 < 90\%$ and $< 85\%$ during non-REM and REM, and d) mean and lowest SpO_2 during respiratory events. CI = confidence interval; REM = rapid eye movement; SpO_2 = peripheral oxygen saturation; TST = total sleep time.

For mean SpO_2 during respiratory events, the same observations as for lowest SpO_2 were made after both single and repeated dosing, ie., no treatment difference after repeated dosing and a slight decrease after single dosing (Table 1, Fig. 1d).

3.3. Influence of daridorexant on sleep-related variables

The influence of daridorexant on sleep duration per h of PSG recording is shown in Fig. 3 and its influence on the number and duration of awakenings is provided in Table 2 and Fig. 4.

After repeated dosing of daridorexant, subjects slept longer during the second, fifth, sixth, and eighth h of PSG recording compared to placebo, ie., mean treatment difference (90% CI) of 6.0 min (0.7, 11.3), 6.4 min (1.3, 11.6), 8.9 min (2.7, 15.0), and 7.2 min (0.6, 13.8), respectively (Fig. 3b). Sleep was also longer after single dosing but to a smaller extent (Fig. 3a).

The number of awakenings was comparable between daridorexant and placebo both after single and repeated dosing (Table 2).

Interestingly, the longest duration of awakenings was reduced after single and repeated dosing with a mean difference (90% CI) of 25.7 min (9.3, 42.2) and 16.2 min (8.5, 23.8), respectively (Table 2, Fig. 4). For mean duration of awakenings, results were comparable to longest duration of awakenings (Table 2, Fig. 4).

4. Discussion

Intermittent and recurrent hypoxemia due to apneas and hypopneas is the main characteristic of OSA and suggested to be the main factor contributing to the adverse long-term consequences of OSA, such as cardiovascular diseases or type-2 diabetes [2,5–8].

Although AHI is the gold standard variable for the diagnosis of OSA [19], the evaluation of nighttime respiration solely based on AHI is considered not sufficient for the evaluation of OSA severity [21,24–26]. Indeed, the proportion of apneas and hypopneas or their duration might vary between individuals having a similar AHI [27] and some studies suggest that an increased duration of apneas

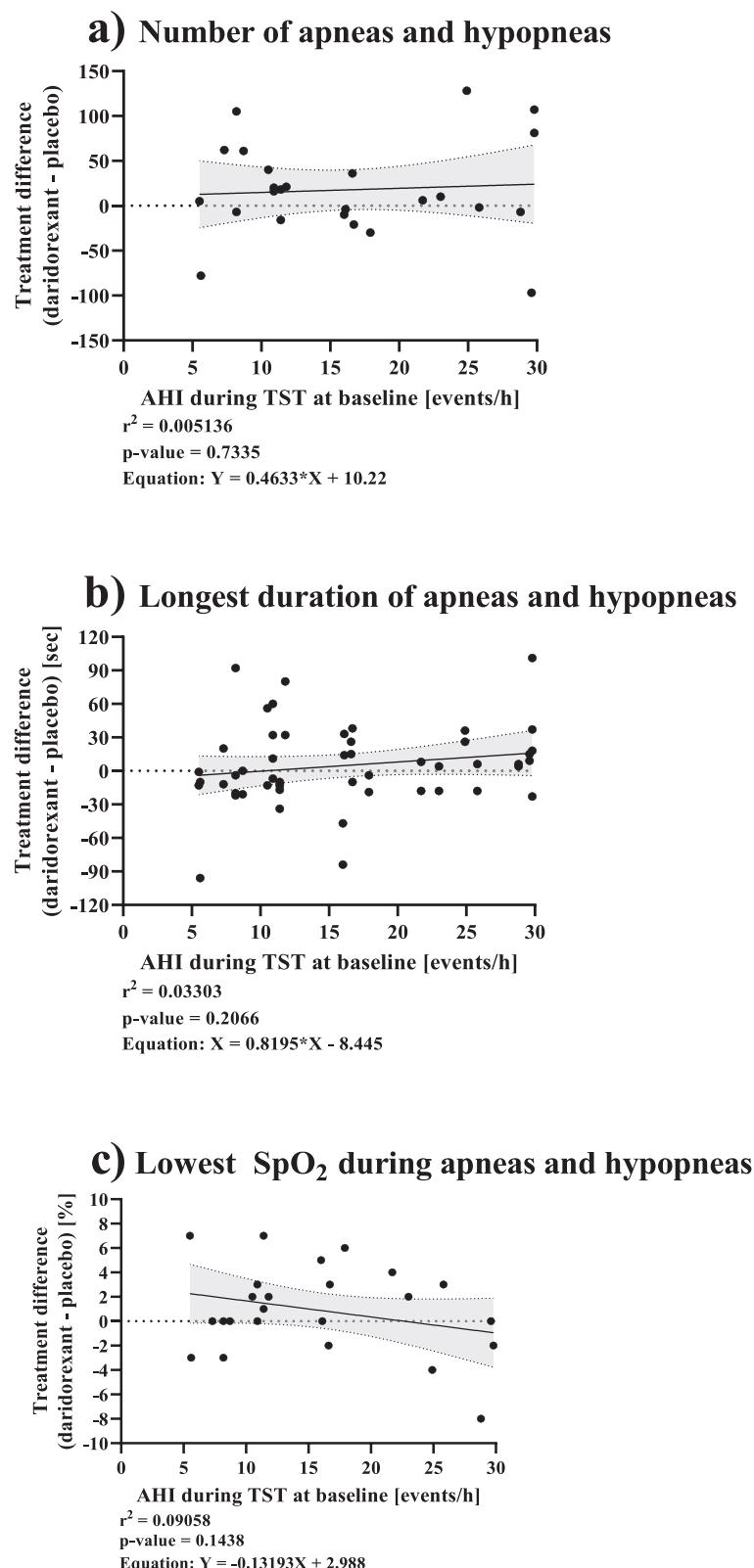


Fig. 2. Linear regression analysis between treatment difference (daridorexant – placebo) for respiration-related variables after repeated dosing and AHI at baseline ($N = 25$). Data are displayed as individual data pairs of treatment difference (daridorexant – placebo) for a) number of apneas + hypopneas during TST, b) longest duration of apneas and hypopneas, and c) lowest SpO_2 during apneas and hypopneas versus OSA severity (AHI during TST at baseline). The grey area indicates the 95% CI of the regression line. AHI = apnea/hypopnea index; CI = confidence interval; OSA = obstructive sleep apnea; r^2 = correlation coefficient; SpO_2 = peripheral oxygen saturation; TST = total sleep time.

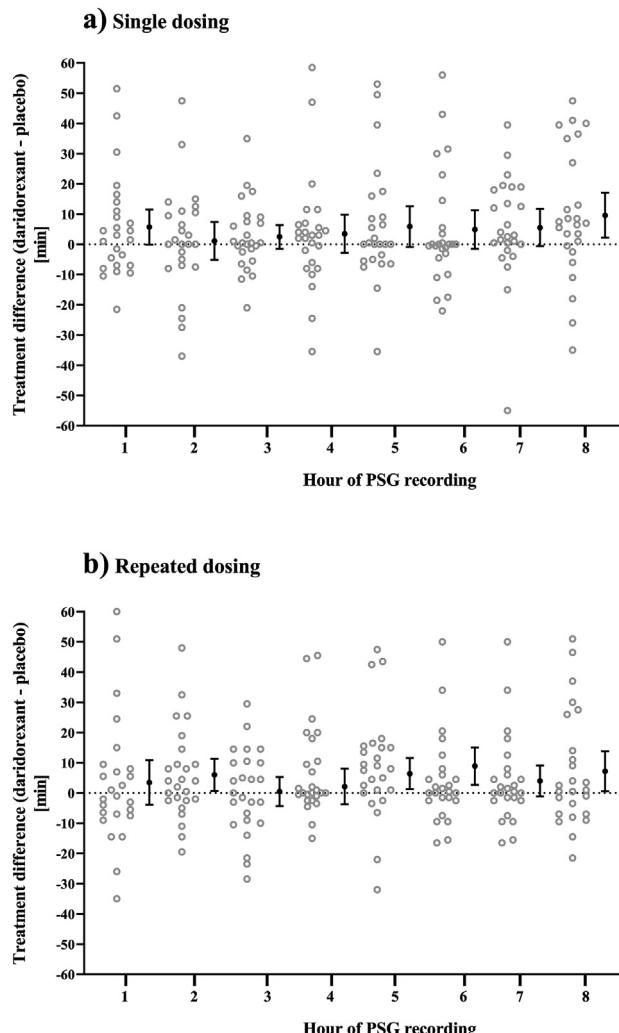


Fig. 3. Individual and mean ($\pm 90\%$ CI) treatment differences for sleep duration per h of PSG recording after single and repeated dosing ($N = 25$). Data are provided as individual (empty circles) and least square means (90% CI; filled circles) for treatment difference (daridorexant – placebo) after a) single (Night 1) and b) repeated dosing (Night 5). CI = confidence interval; PSG = polysomnography.

and hypopneas might contribute to the long-term increased risk of developing cardiovascular diseases in patients with OSA [28–30]. It has also been proposed that sleep hypoventilation may be better reflected by the lowest SpO₂ during respiratory events rather than SpO₂ during sleep [21].

In the present evaluation, more respiratory events were observed during TST both after single and repeated dosing of

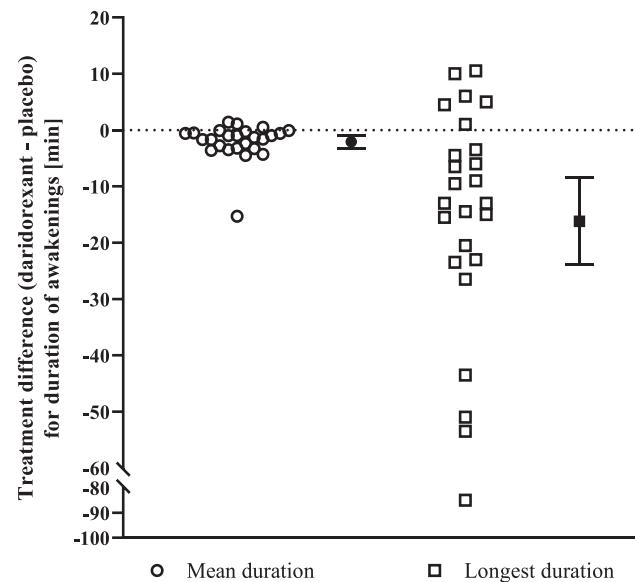


Fig. 4. Individual and mean ($\pm 90\%$ CI) treatment differences for duration of awakenings after repeated dosing ($N = 25$). Data are provided as individual (empty circles/squares) and least square means (90% CI; filled circles/squares) for treatment difference (daridorexant – placebo) after repeated dosing (Night 5). CI = confidence interval.

daridorexant compared to placebo. This increase is mainly explained by the concomitant prolongation of TST by approximately 40 min observed after daridorexant administration compared to placebo. However, normalization by sleep time of the total number of events provides similar AHI values after daridorexant and placebo administration [18]. After single and repeated dosing of daridorexant, the proportion of apneas and hypopneas was similar for daridorexant and placebo suggesting no shift from hypopneas to apneas. Moreover, the duration of these events was also not affected. Finally, the lowest SpO₂ during respiratory events was comparable between daridorexant and placebo although a slightly lower value was observed after single dosing.

The increased number of events observed during non-REM and N2 sleep stages after daridorexant administration corresponds to the increased time spent in these sleep stages [18], however, has no impact on oxygen saturation as SpO₂-related variables were comparable between daridorexant and placebo.

As for AHI during TST [18], no association between disease severity (ie., AHI at baseline) and treatment differences for the number and longest duration of apneas and hypopneas as well as for the lowest SpO₂ was observed. This was applicable to both single and repeated dosing and is suggestive of a limited effect, if any, on nighttime respiratory function in a more severe OSA population although this remains to be confirmed in a dedicated study.

Table 2
Influence of daridorexant on the number and duration of awakenings.

	Single dosing			Repeated dosing for 5 days ^a		
	Daridorexant (50 mg)	Placebo	Treatment difference (daridorexant – placebo)	Daridorexant (50 mg)	Placebo	Treatment difference (daridorexant – placebo)
Number of awakenings	22.3 (19.2, 25.3)	22.1 (19.1, 25.2)	0.10 (-3.20, 3.40)	23.6 (20.6, 26.6)	23.2 (20.1, 26.2)	0.40 (-2.80, 3.60)
Duration of awakenings [min]						
Mean	2.9 (0.7, 5.0)	6.3 (4.2, 8.4)	-3.4 (-6.1, -0.7)	2.8 (2.0, 3.5)	4.8 (4.0, 5.6)	-2.1 (-3.2, -0.9)
Longest	17.8 (6.0, 29.6)	43.5 (31.7, 55.3)	-25.7 (-42.2, -9.3)	17.0 (10.8, 23.1)	33.1 (27.0, 39.2)	-16.2 (-23.8, -8.5)

Data are displayed as least squares mean (95% CI) for treatments and (90% CI) for treatment difference.

CI = confidence interval.

^a Study treatments were administered once daily in the evening.

Taken together, these contributive data regarding the mechanistic role of daridorexant on ventilatory control suggest that daridorexant does not increase disease severity and is not expected to cause an increased risk for patients with insomnia having either mild or moderate OSA.

With regard to sleep, daridorexant prolonged TST despite absence of insomnia in the studied population of patients with mild to moderate OSA and also improved other sleep characteristics, ie., shortened wake time after sleep onset (WASO) [18]. Shortening of WASO can be explained by a reduced number of awakenings and/or a shorter duration of awakenings. The latter was observed after daridorexant administration mainly in the second part of the night. Reduction of duration of awakenings by approximately 20 min and the increased sleep duration in the second part of the night are relevant for patients with OSA that are known to have difficulties in maintaining sleep. This might also be suggestive of a favorable effect of daridorexant in patients with OSA showing low adherence to CPAP as these patients are known to usually switch off their device earlier than patients adherent to this device [31,32]. This favorable effect would however need to be confirmed in a dedicated study in patients with OSA using CPAP.

5. Conclusions

This is to our best knowledge the first study that extensively evaluated the influence of a DORA on nighttime respiration and sleep in patients with mild to moderate OSA. The evaluation of different indices of OSA severity and sleep is suggestive of a safe use of daridorexant administered at the highest Phase 3 dose of 50 mg in patients with mild to moderate OSA as well as a favorable modulation of sleep in this population.

Author contributions

Marie-Laure Boof, Mike Ufer, and Jasper Dingemanse designed the study. Ingo Fietze, as Principal investigator, conducted the study and was responsible for data acquisition. Anne-Sophie Guern and Vincent Lemoine performed the statistical analyses. Marie-Laure Boof drafted the manuscript and Mike Ufer, Ingo Fietze, Jean-Louis Pépin, and Jasper Dingemanse critically revised the manuscript. All authors gave the final approval of the manuscript to be published.

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Conflict of interest

Marie-Laure Boof, Mike Ufer, Anne-Sophie Guern, Vincent Lemoine, and Jasper Dingemanse are employees of Idorsia Pharmaceuticals Ltd, Ingo Fietze was the Principal investigator of the study, and Jean-Louis Pépin provided scientific advice.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2021.11.015>.

References

- [1] Dempsey JA, Veasey SC, Morgan BJ, et al. Pathophysiology of sleep apnea. *Physiol Rev* 2010;90(1):47–112. <https://doi.org/10.1152/physrev.00043.2008>.
- [2] Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Prim* 2015;1:15015. <https://doi.org/10.1038/nrdp.2015.15>.
- [3] Ward KL, Hillman DR, James A, et al. Excessive daytime sleepiness increases the risk of motor vehicle crash in obstructive sleep apnea. *J Clin Sleep Med* 2013;9(10):1013–21. <https://doi.org/10.5664/jcsm.3072>.
- [4] Baldwin CM, Griffith KA, Nieto FJ, et al. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep* 2001;24(1):96–105. <https://doi.org/10.1093/sleep/24.1.96>.
- [5] McNicholas WT, Bonsignore MR. Management Committee of EU COST ACTION B26. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007;29(1):156–78. <https://doi.org/10.1183/09031936.00027406>.
- [6] Tkacova R, McNicholas WT, Vavrosky M, et al. European Sleep Apnoea Database study collaborators. Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. *Eur Respir J* 2014;44(4):931–41. <https://doi.org/10.1183/09031936.00225113>.
- [7] Kendzerska T, Gershon AS, Hawker G, et al. Obstructive sleep apnea and incident diabetes: A historical cohort study. *Am J Respir Crit Care Med* 2014;190(2):218–25. <https://doi.org/10.1164/rccm.201312-2209OC>.
- [8] Nagayoshi M, Punjabi NM, Selvin E, et al. Obstructive sleep apnea and incident type 2 diabetes. *Sleep* 2016;25:156–61. <https://doi.org/10.1016/j.sleep.2016.05.009>.
- [9] Janssen HCJP, Venekamp LN, Peeters GAM, et al. Management of insomnia in sleep disordered breathing. *Eur Respir Rev* 2019;28(153). <https://doi.org/10.1183/16000617.0080-2019>.
- [10] Sweetman A, Lack L, Bastien C. Co-morbid insomnia and sleep apnea (COMISA): prevalence, consequences, methodological considerations, and recent randomized controlled trials. *Brain Sci* 2019;9(12). <https://doi.org/10.3390/brainsci9120371>.
- [11] Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7(8):687–98. [https://doi.org/10.1016/S2213-2600\(19\)30198-5](https://doi.org/10.1016/S2213-2600(19)30198-5).
- [12] Muehlan C, Vaillant C, Zenklusen I, et al. Clinical pharmacology, efficacy, and safety of orexin receptor antagonists for the treatment of insomnia disorders. *Expert Opin Drug Metabol Toxicol* 2020;6(11):1063–78. <https://doi.org/10.1080/17425255.2020.1817380>.
- [13] Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci* 2007;8:171–81. <https://doi.org/10.1038/nrn2092>.
- [14] Belsonra® US Package Insert. United States food and drug administration full prescribing information. Revised: 3/2021 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204569s008lbl.pdf.
- [15] Dayvigo® US Package Insert. United States food and drug administration full prescribing information. Revised: 12/2019 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf.
- [16] Dauvilliers Y, Zammitt G, Fietze I, et al. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. *Ann Neurol* 2020;87(3):347–56. <https://doi.org/10.1002/ana.25680>.
- [17] Zammitt G, Dauvilliers Y, Pain S, et al. Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder. *Neurology* 2020;94(21):e2222–32. <https://doi.org/10.1212/WNL.0000000000009475>.
- [18] Boof ML, Dingemanse J, Lederer K, et al. Effect of the new dual orexin receptor antagonist daridorexant on nighttime respiratory function and sleep in patients with mild and moderate obstructive sleep apnea. *Sleep* 2021;44(6). <https://doi.org/10.1093/sleep/zsaa275>, aop.
- [19] Kapur VK, Ackley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017;13(3):479–504. <https://doi.org/10.5664/jcsm.6506>.
- [20] Mason M, Cates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. *Cochrane Database Syst Rev* 2015. <https://doi.org/10.1002/14651858.CD011090.pub2>.
- [21] Peppard PE, Hagen EW. The last 25 Years of obstructive sleep apnea epidemiology-and the next 25? *Am J Respir Crit Care Med* 2018;197(3):310–2. <https://doi.org/10.1164/rccm.201708-1614PP>.
- [22] American Academy of Sleep Medicine Practice guidelines. Available from: <https://aasm.org/clinical-resources/practice-standards/>.
- [23] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Rep Am Acad Sleep Med Task Force*. *Sleep* 1999;22(5):667–869.
- [24] Sarac S, Afşar GC. Effect of mean apnea-hypopnea duration in patients with obstructive sleep apnea on clinical and polysomnography parameter. *Sleep Breath* 2020;24(1):77–81. <https://doi.org/10.1007/s11325-019-01870-y>.
- [25] Pevernagie DA, Gnidovec-Strazisar B, Grote I, et al. On the rise and fall of the apnea-hypopnea index: a historical review and critical appraisal. *J Sleep Res* 2020;29(4):e13066. <https://doi.org/10.1111/jsr.13066>.
- [26] Lévy P, Tamisier R, Pépin JL. Assessment of sleep-disordered-breathing: quest for a metric or search for meaning? *J Sleep Res* 2020;29(4):e13143. <https://doi.org/10.1111/jsr.13143>.

- [27] Muraja-Murro A, Nurkkala J, Tiihonen P, et al. Total duration of apnea and hypopnea events and average desaturation show significant variation in patients with a similar apnea-hypopnea index. *J Med Eng Technol* 2012;36:393–8.
- [28] Chouchou F, Pichot V, Barthélémy JC, et al. Cardiac sympathetic modulation in response to apneas/hypopneas through heart rate variability analysis. *PLoS One* 2014;9(1):e86434. <https://doi.org/10.1371/journal.pone.0086434>.
- [29] Sola-Soler J, Giraldet BF, Fiz JA, et al. Relationship between heart rate excursion and apnea duration in patients with Obstructive Sleep Apnea. *Annu Int Conf IEEE Eng Med Biol Soc* 2017;2017:1539–42. <https://doi.org/10.1109/EMBC.2017.8037129>.
- [30] Hietakoste S, Korkalainen H, Kainulainen S, et al. Longer apneas and hypopneas are associated with greater ultra-short-term HRV in obstructive sleep apnea. *Sci Rep* 2020;10(1):21556. <https://doi.org/10.1038/s41598-020-77780-x>.
- [31] Grewe FA, Bradicich M, Gaisl T, et al. Patterns of nightly CPAP usage in OSA patients with suboptimal treatment adherence. *Sleep Med* 2020;74:109–15. <https://doi.org/10.1016/j.sleep.2020.05.042>.
- [32] Pépin JL, Bailly S, Rinder P, et al. CPAP therapy termination rates by OSA phenotype: a French nationwide database analysis. *J Clin Med* 2021;10(5):936. <https://doi.org/10.3390/jcm10050936>.