Daridorexant, a New Dual Orexin Receptor Antagonist to Treat Insomnia Disorder

Yves Dauvilliers, MD, PhD,[1] Gary Zammit, PhD,[2] Ingo Fietze, MD,[3] David Mayleben, PhD,[4] Dalma Seboek Kinter, PhD,[5] Scott Pain, MSc,[5] and Jan Hedner, MD, PhD[6]

Objective: To evaluate the dose–response relationship of daridorexant, a new dual orexin receptor antagonist, on sleep variables in subjects with insomnia disorder.
Methods: Adults (≤64 years) with insomnia disorder were randomized (1:1:1:1:1:1) to receive daily oral placebo, daridorexant (5, 10, 25, or 50mg), or 10mg zolpidem for 30 days. The primary efficacy outcome was the change in wake time after sleep onset from baseline to days 1 and 2. Secondary outcome measures were change in latency to persistent sleep from baseline to days 1 and 2, change in subjective wake time after sleep onset, and subjective latency to sleep onset from baseline to week 4. Safety was also assessed.
Results: Of 1,005 subjects screened, 359 (64% female) were randomized and received ≥1 dose. A significant dose–response relationship (multiple comparison procedure-modeling, 2-sided $p < 0.001$) was found in the reduction of wake after sleep onset and latency to persistent sleep from baseline to days 1 and 2 with daridorexant. These reductions were sustained through to days 28 and 29 ($p = 0.050$ and $p = 0.042$, respectively). Similar dose-dependent relationships were observed for subjective wake after sleep onset and subjective latency to sleep onset. The incidence of treatment-emergent adverse events was 35%, 38%, 38%, and 34% in subjects treated with 5, 10, 25, and 50mg daridorexant, respectively, compared with 30% for placebo, and 40% for 10mg zolpidem. There were no clinically relevant treatment-related serious adverse events. Four subjects withdrew due to adverse events.
Interpretation: Daridorexant induced a dose-dependent reduction in wake time after sleep onset in subjects with insomnia disorder (Clinicaltrials.gov NCT02839200).

ANN NEUROL 2020;87:347–356

Insomnia disorder is a common sleep disorder associated with several comorbidities and major economic and societal impacts. Current guidelines recommend psychological and pharmacological therapies to reduce the time to fall asleep and the time spent awake after sleep onset, with subsequent improvements in daytime functioning.[1–4] Among pharmacological approaches, benzodiazepines, Z-drugs, melatonin receptor agonists, and sedating antidepressants have been frequently used options for insomnia,[5] but typically are not effective enough.[1] Furthermore, currently available sleep medications that adequately address problems with sleep maintenance may be associated with common side effects of somnolence and drowsiness.[6] Therefore, there is a delicate balance between the pharmacodynamic efficacy of sleep medications and the potential to impart residual effects. The identification of the wakefulness orexin (hypocretin) signaling pathway offers promising therapeutic strategies with orexin receptor antagonists. Suvorexant, a dual orexin receptor antagonist (DORA), was first approved in 2014 for the treatment of insomnia and is now approved in several countries.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25680

Received Jul 7, 2019, and in revised form Jan 13, 2020. Accepted for publication Jan 13, 2020.

Address correspondence to Dr Dauvilliers, Unité du Sommeil, Département de Neurologie, Hôpital Gui-de-Chauliac, Université Montpellier, INSERM, U1061, Montpellier, France. E-mail: y-dauvilliers@chu-montpellier.fr

From the [1]Sleep Unit, Department of Neurology, Neuropsychiatry: Epidemiological and Clinical Research, University of Montpellier, National Institute of Health and Medical Research, Montpellier University Hospital Center, Montpellier, France; [2]Clinilabs Drug Development Corporation and Icahn School of Medicine at Mount Sinai, New York, NY; [3]Center of Interdisciplinary Sleep Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany; [4]CTI Clinical Research Center, Cincinnati, OH; [5]Clinical Development, Idorsia Pharmaceuticals, Allschwil, Switzerland; and [6]Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

Additional supporting information can be found in the online version of this article.

© 2020 American Neurological Association

Suvorexant reduces latency to sleep onset (LSO) and time to wake after sleep onset (WASO) without disrupting sleep architecture.[7] Positive effects were mostly seen at doses higher than currently approved,[8,9] although tolerability issues such as next-morning residual effects increase with increasing dose.[10] Thus, a need remains for a well-tolerated sleep medication to treat insomnia disorder that addresses nighttime insomnia symptoms without negatively impacting next-day functioning.

Daridorexant (ACT-541468) is the result of a tailored discovery program aimed at identifying a sleep-promoting agent with appropriate duration of action, sufficient for covering the night but avoiding next-morning residual activity at optimal efficacious doses. It was selected based on physiology-based pharmacokinetic (PK) and pharmacodynamic (PD) modeling of 20 structural analogs out of >25,000 molecules synthesized. Human simulations of daridorexant suggested high and rapid peak orexin receptor occupancy and fast decline in receptor occupancy at a dose of 25mg.[11]

Verifying model predictions, clinical studies in young and elderly healthy subjects who received daridorexant at doses ranging from 5 to 200mg showed a favorable safety profile.[12,13] The half-life was around 6 hours, and maximum plasma concentration occurred between 0.8 and 2 hours postdosing.[14] Based on early clinical data, daridorexant may be a promising candidate for the treatment of insomnia disorder. This study aimed to evaluate the efficacy and safety of daridorexant on objective and subjective sleep parameters in subjects with insomnia disorder.

Subjects and Methods

Study Design

This randomized, double-blind, placebo-controlled, and active-controlled dose–response phase 2 study was conducted at 38 sites in 6 countries at hospitals and sleep centers in Germany, Hungary, Israel, Spain, Sweden, and the USA. The study was approved by the appropriate health authority, ethics committee, or institutional review board for each participating site. This study is registered on Clinicaltrials.gov (NCT02839200) and EudraCT (2016-000826-21).

Subjects

All subjects provided written informed consent prior to enrolment in the study, which was conducted in accordance with the Declaration of Helsinki.

Demographic characteristics including age, sex, and race were collected. Race was classified and defined by the investigator and included to assess any differences between races.

Eligible subjects were men and women 18 to 64 years of age who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for insomnia disorder.[15] Subjects were required to have a self-reported history of ≥30 minutes LSO, ≥30 minutes WASO, a total sleep time (TST) ≤ 6.5 hours on at least 3 of 7 consecutive nights, and a bedtime between 21:30 and 00:30 hours.

A screening period of 14 to 28 days, including a single-blind run-in phase, was followed by a 30-day double-blind treatment period, a single-blind placebo run-out for 1 day, and a 30-day safety follow-up period (Fig 1).

During the screening phase, subjects completed a daily sleep diary for at least 7 consecutive days to assess baseline sleep characteristics. Polysomnography (PSG) was recorded during 2 consecutive, single-blind, placebo-treated nights. Subjects needed to meet

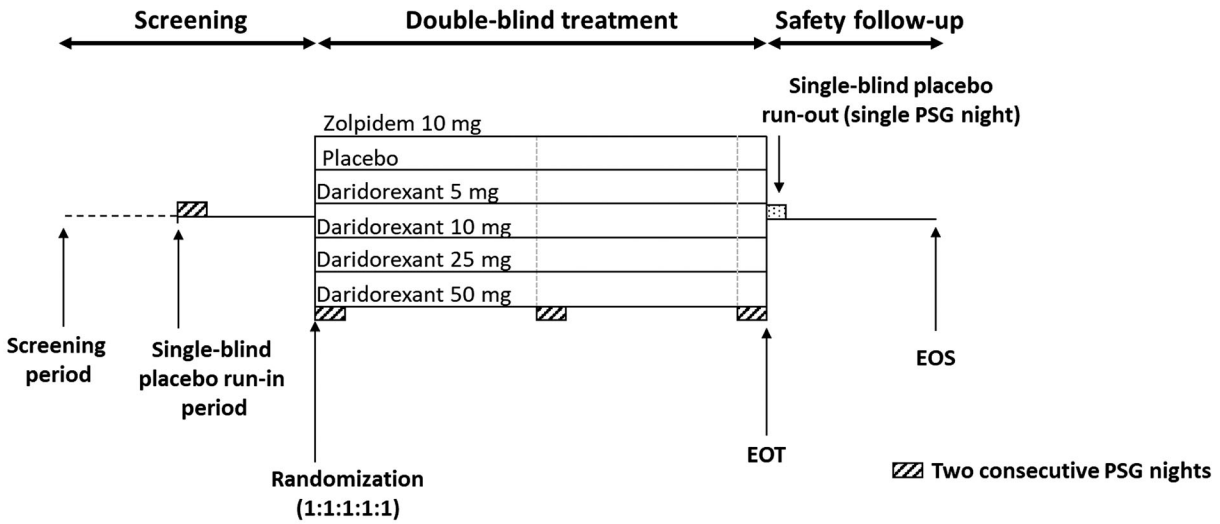

FIGURE 1: Study design. The study comprised a screening period (including a single-blind placebo run-in phase), followed by a treatment phase, a single-blind placebo run-out period, and a safety follow-up period. EOS = end of study; EOT = end of treatment; PSG = polysomnography.

the following PSG criteria for randomization: mean of 2 nights WASO ≥30 minutes, latency to persistent sleep (LPS) ≥ 30 minutes, and TST < 420 minutes. Subjects had to have an Insomnia Severity Index (ISI) score of at least 15.

Subjects with lifetime suicidal behavior, suicidal ideation, unstable medical condition, or significant medical disorder (ie, depression and anxiety) assessed by clinical judgment that could interfere with safety, treatment compliance, and study assessments were excluded. Other exclusion criteria included ongoing sleep disorders other than insomnia, treatment with a central nervous system–active drug, and cognitive behavior therapy for insomnia within 1 month prior to study start. Subjects were excluded before randomization based on occurrence of an apnea or hypopnea event above 10 per hour.[16]

Randomization and Masking

Eligible subjects were centrally randomized using an interactive web response system in a 1:1:1:1:1:1 ratio to 1 of the 6 treatment arms: placebo (0mg), 5, 10, 25, or 50mg daridorexant, or 10mg zolpidem. The randomization list was generated independently and kept strictly confidential. A double-dummy procedure was implemented to ensure blinding. Study treatment comprised 2 capsules for each intake: daridorexant, placebo capsules matching daridorexant, overencapsulated zolpidem, or placebo capsules matching overencapsulated zolpidem.

Procedures

Treatment was in the form of capsules taken orally every evening at least 2 hours after last meal during the double-blind treatment period of 29 days. Treatment was taken 30 minutes before lights off on PSG nights.

Two consecutive PSG nights were performed at screening to provide a baseline then at days 1 and 2, days 15 and 16, days 28 and 29, and a single PSG night at day 30 following standard methods[17] to objectively assess sleep variables. WASO (defined as the time [in minutes] spent awake between the onset of persistent sleep and lights on) and LPS (defined as time [in minutes] from lights off to persistent sleep) from each overnight PSG recording were scored centrally. All PSG parameters were averaged over 2 consecutive recording nights (except for the day 30 single PSG). Daily self-administered subject diaries in the morning and in the evening assessed subjective sleep parameters: subjective WASO (sWASO; defined as time [in minutes] spent awake after sleep onset), subjective LSO (sLSO; defined as time [in minutes] to fall asleep), and subjective TST (sTST; defined as time [in minutes] of total sleep duration). All diary recordings were averaged over 7 days, at baseline, and during each week of the 4-week treatment period. Self-reported quality of sleep and morning sleepiness, and self-reported daytime alertness and daytime ability to function were collected by visual analog scales (VASs) in the morning and evening, respectively, as part of the sleep diary. ISI was completed at baseline and at the end of double-blind treatment.[18]

Outcomes

The primary efficacy outcome measure was change in WASO from baseline (mean of the 2 values of the run-in PSGs) to days 1 and 2. Secondary efficacy outcome measures were change in LPS from baseline to days 1 and 2 and change in sWASO and sLSO from baseline recording to week 4 average. Other efficacy outcome measures included the change from baseline to all timepoints of measurement in WASO, LPS, TST, sWASO, sLSO, sTST, sleep quality assessed by VAS, and ISI scores.

Safety and tolerability were assessed by adverse event (AE) reports, physical examination, changes in vital signs, electrocardiograms (ECGs), and clinical laboratory reports. Potential next-morning sleepiness was assessed in the morning after each PSG night with VASs, the Karolinska Sleepiness Scale (KSS),[19] the Sheehan Disability Scale (SDS),[20] the Digit Symbol Substitution Test (DSST),[21,22] and neurological examinations (analysis of gait, tandem walking, Romberg test). Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)[21] at each visit. An independent safety board (ISB) blindly reviewed and adjudicated potential AEs of special interest (AESIs) temporally associated with the use of study treatment. AESIs were predefined as preferred term-coded AEs related to narcolepsylike events, complex sleep behavior events, and suicidal thoughts and/or behaviors.

Rebound insomnia was assessed as the change from baseline to single-blind placebo day 30 PSG night parameters (WASO, LPS, and TST). Withdrawal symptoms were collected during the 24 hours following study treatment discontinuation using Benzodiazepine Withdrawal Symptom Questionnaire[22] scores.

Statistical Analysis

Assuming the maximum mean reduction in WASO from baseline to days 1 and 2 (primary endpoint) with a daridorexant dose was 25 minutes longer than with placebo (standard deviation [SD] = 40 minutes), with values from 8% of subjects not available for analysis, a total sample size of approximately 250 (ie, 50 subjects per arm) would provide between 89 and 92% power (power of 90% when averaged over all dose–response models) to reject the null hypothesis (absence of a dose–response relationship) with a 2-sided 5% type I error.[23]

The primary endpoint was analyzed using the modified full analysis set (FAS). This comprised all subjects from the FAS (all randomized subjects who received at least 1 dose of double-blind study treatment) who had at least 1 WASO assessment at baseline and at days 1 and 2. All subjects who received at least 1 dose of double-blind study treatment were included in the safety set. Analyses of rebound insomnia and withdrawal symptoms were performed on the subset of subjects who received the 1 dose of single-blind placebo treatment in the run-out period.

The dose–response relationship of daridorexant for the primary and secondary outcome measures was analyzed with the multiple comparison procedure-modeling (MCP-Mod) method.[24,25] The best-fit model was selected from a set of 4 predefined candidate dose–response models chosen to represent the possible shapes

anticipated for the dose–response relationship: Emax1 (90% of effect at 10mg), Emax2 (80% of effect at 15mg), Emax3 (40% of effect at 10mg), and Linear. For each model, the null hypothesis was tested against the alternative hypothesis (existence of a dose–response relationship). The statistically significant models were fitted to the least squares (LS) mean estimates and associated variance–covariance generated from the analysis of covariance model, with fixed effects for treatment and sex, and baseline values as covariates. The best-fit model (Emax or Linear) was selected based on the smallest Akaike information criterion value and used to characterize the dose–response relationship.

For the primary outcome measure, 2-sided p values <0.05 were considered statistically significant. No adjustments for multiplicity were made for secondary outcome measures. Effects with zolpidem compared with placebo were analyzed separately and considered exploratory.

Descriptive statistics were provided for all exploratory variables either as frequency and percentage for categorical variables or

TABLE 1. Subject Demographics and Baseline Characteristics

		Daridorexant					
Characteristic	**Placebo, 0mg, n = 60**	**5mg, n = 60**	**10mg, n = 58**	**25mg, n = 60**	**50mg, n = 61**	**Zolpidem 10mg, n = 60**	**Total, N = 359**
Sex, n (%)							
M	22 (37)	22 (37)	20 (34)	21 (35)	22 (36)	22 (37)	129 (36)
F	38 (63)	38 (63)	38 (66)	39 (65)	39 (64)	38 (63)	230 (64)
Mean age, yr (SD)	45.7 (10.4)	42.4 (11.4)	45.2 (10.9)	46.4 (11.9)	45.0 (11.5)	43.7 (11.8)	44.7 (11.3)
Mean BMI, kg/m^2 (SD)	25.4 (3.3)	24.9 (3.2)	25.4 (3.4)	24.9 (3.3)	24.5 (2.9)	26.0 (3.5)	25.2 (3.3)
Race, n (%)							
Caucasian	52 (87)	54 (90)	49 (84)	56 (93)	56 (92)	54 (90)	321 (89)
Black or African American	7 (12)	5 (8)	8 (14)	4 (7)	5 (8)	6 (10)	35 (10)
Asian	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Native Hawaiian/other Pacific Islander	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (0.3)
Other	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)
Objective sleep parameters, mean min (SD)							
WASO	95.8 (34.7)	97.4 (47.1)	98.8 (36.3)	99.6 (40.9)	94.0 (31.9)	99.2 (38.8)	97.5 (38.6)
LPS	74.3 (39.3)	72.7 (51.9)	66.1 (31.8)	74.3 (43.5)	69.6 (30.2)	73.4 (34.8)	71.8 (39.3)
TST	317.7 (53.9)	317.8 (73.6)	322.4 (50.4)	313.7 (57.1)	323.3 (45.6)	315.8 (54.9)	318.45 (26.6)
Subjective sleep parameters, mean (SD)							
sWASO, min	79.4 (37.2)	86.2 (43.5)	84.8 (45.4)	77.6 (43.7)	78.1 (46.7)	76.2 (41.1)	80.4 (43.0)
sLSO, min	55.0 (22.6)	56.8 (29.6)	59.5 (29.6)	53.9 (24.5)	58.5 (30.5)	51.7 (24.9)	55.9 (27.1)
sTST, min	322.3 (55.1)	316.8 (49.2)	307.1 (54.8)	317.2 (54.9)	315.0 (48.7)	322.1 (52.6)	316.8 (52.6)
ISI	21.3 (2.7)	20.8 (2.6)	21.2 (3.3)	21.3 (2.7)	21.1 (2.7)	21.3 (2.9)	21.2 (2.8)

BMI = body mass index; F = female; ISI = Insomnia Severity Index; LPS = latency to persistent sleep; M = male; SD = standard deviation; sLSO = subjective latency to sleep onset; sTST = subjective TST; sWASO = subjective WASO; TST = total sleep time; WASO = wake after sleep onset.

using descriptive statistics for continuous variables. Occurrences of AEs and serious AEs (SAEs) and change in laboratory markers, questionnaires, VASs, ECGs, and vital signs were summarized using descriptive statistics.

Results

Between October 4, 2016 and June 20, 2017, a total of 1,005 subjects were screened. Of 360 randomized subjects, 359 received at least 1 dose of double-blind study treatment. Subject demographics were comparable across treatment groups (Table 1). The majority of subjects were female (n = 230, 64%), and Caucasian (n = 321, 89%). The mean age (±SD) at screening was 44.7 years (±11.3), and mean body mass index (±SD) was 25.2 (±3.3kg/m^2). Baseline sleep parameters were similar across the treatment groups (Table 1). Most subjects (94%) completed the 30-day treatment period and received the single-blind placebo run-out treatment. Treatment discontinuation was not related to dose or treatment group.

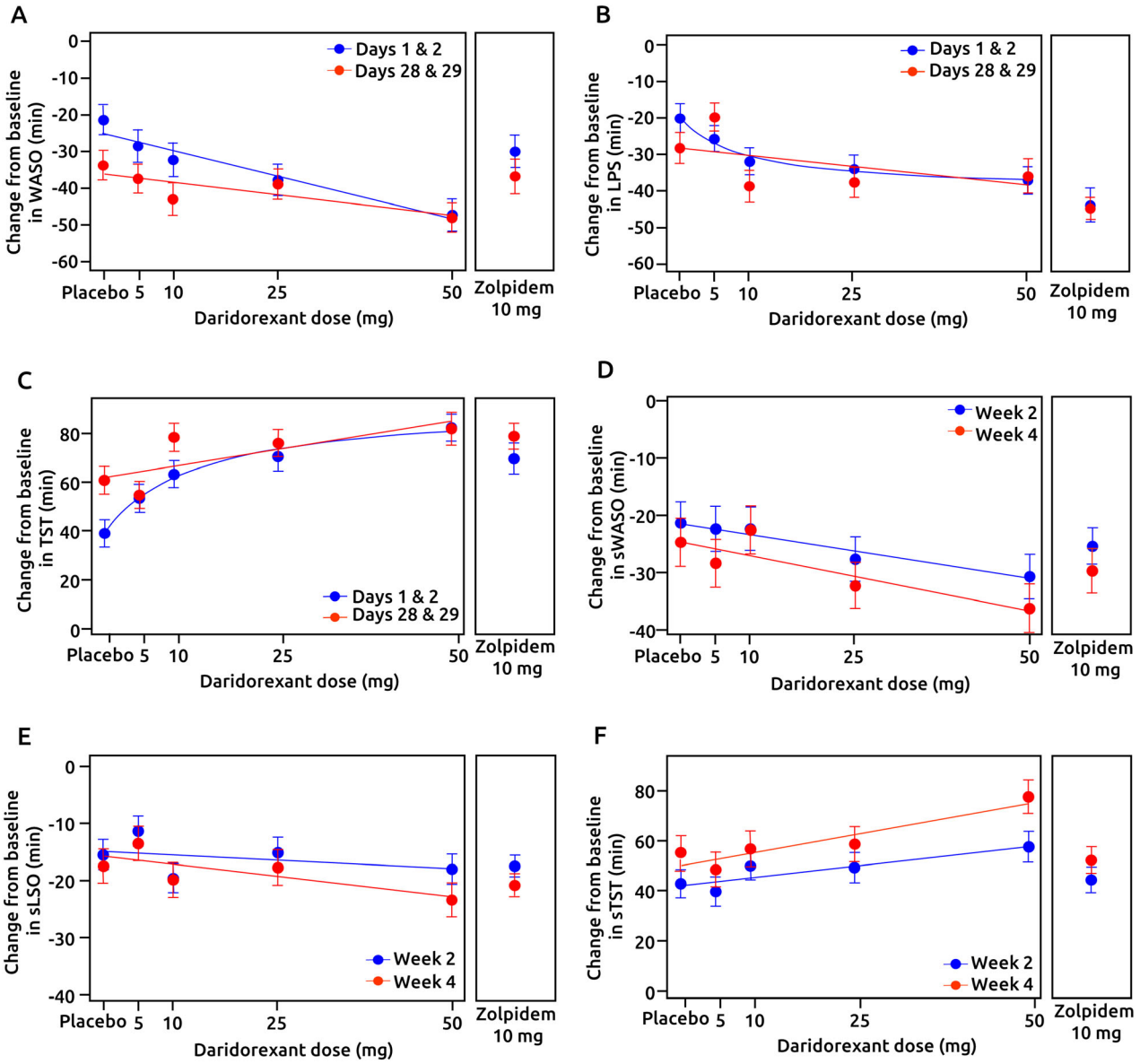

FIGURE 2: Objective and subjective sleep parameters. (A–C) Change in wake after sleep onset (WASO; A), latency to persistent sleep (LPS; B), and total sleep time (TST; C) from baseline to days 1 and 2 (blue lines) and days 28 and 29 (red lines) according to dose of daridorexant. (D–F) Change in subjective WASO (sWASO; D), subjective latency to sleep onset (sLSO; E), and subjective TST (sTST; F) from baseline to week 2 (blue lines) and week 4 (red lines) according to dose of daridorexant. The change in the measured sleep parameters with 10mg zolpidem is shown on the right for comparison. Data are presented as least squares mean ± standard error.

Efficacy

A significant ($p < 0.001$, MCP-Mod method) dose–response relationship in the reduction of WASO from baseline to days 1 and 2 was established for daridorexant (Fig 2, Table 2). The effect of daridorexant on WASO was sustained at days 15 and 16 (see Supplementary Table 1) and days 28 and 29. Placebo-corrected LS mean estimates of change from baseline to days 1 and 2 in WASO were also calculated (Supplementary Table 2).

A significant dose–response relationship was observed in the reduction of LPS from baseline to days 1 and 2 ($p < 0.001$), showing sustained effects at days 15 and 16 (see

TABLE 2. Objective and Subjective Sleep Parameters

Efficacy endpoints,	Change from Baseline to Timepoint	Placebo, 0mg, n = 60	Daridorexant 5mg, n = 60	Daridorexant 10mg, n = 58	Daridorexant 25mg, n = 60	Daridorexant 50mg, n = 61	Zolpidem, 10mg, n = 60[a]
Objective sleep parameters, min							
WASO	Days 1 and 2	−21.4 (4.2)	−28.4 (4.2)	−32.3 (4.3)	−37.7 (4.3)	−47.1 (4.2)	−29.9 (4.3)
	Days 28 and 29	−33.8 (4.2)	−37.5 (4.1)	−42.8 (4.3)	−38.9 (4.2)	−48.0 (4.1)	−36.5 (4.4)
LPS	Days 1 and 2	−20.1 (3.8)	−25.9 (3.8)	−32.0 (3.9)	−34.2 (3.8)	−37.2 (3.8)	−44.0 (4.7)
	Days 28 and 29	−28.4 (4.3)	−20.2 (4.2)	−38.7 (4.4)	−37.9 (4.3)	−35.8 (4.3)	−45.1 (3.3)
TST	Days 1 and 2	38.2 (5.6)	52.7 (5.6)	62.4 (5.7)	69.7 (5.6)	81.4 (5.6)	68.8 (6.3)
	Days 28 and 29	60.0 (5.6)	53.9 (5.5)	77.4 (5.7)	75.1 (5.6)	81.6 (5.5)	78.0 (5.1)
Subjective sleep parameters							
sWASO, min	Week 2	−22.0 (3.9)	−22.8 (3.9)	−22.9 (3.8)	−28.2 (3.9)	−31.2 (3.8)	−26.0 (3.4)
	Week 4	−25.2 (4.2)	−28.9 (4.2)	−23.3 (4.4)	−32.9 (4.1)	−36.8 (4.3)	−30.2 (3.9)
sLSO, min	Week 2	−15.6 (2.7)	−11.5 (2.7)	−19.9 (2.8)	−15.3 (2.7)	−18.2 (2.7)	−17.7 (2.0)
	Week 4	−17.5 (3.0)	−13.7 (2.9)	−20.1 (3.1)	−17.9 (3.0)	−23.5 (3.0)	−20.9 (2.0)
sTST, min	Week 2	41.4 (45.0)	40.1 (47.6)	52.0 (44.7)	48.9 (54.7)	57.0 (41.9)	44.7 (36.0)
	Week 4	52.7 (50.3)	48.3 (56.2)	59.1 (54.1)	56.2 (51.5)	77.4 (58.7)	53.2 (35.5)
ISI, mean (SD)	Day 30	−7.7 (5.4)	−7.4 (6.2)	−8.1 (5.8)	−7.9 (5.9)	−8.5 (6.3)	−9.0 (5.0)
Self-reported VAS scores, mean mm (SD)							
Sleep quality	Week 2	12.8 (14.7)	11.9 (15.5)	13.3 (11.9)	16.1 (17.2)	14.3 (14.6)	15.4 (13.7)
	Week 4	19.0 (18.0)	17.4 (19.8)	17.0 (16.7)	21.3 (19.2)	20.9 (17.7)	19.3 (15.6)
Morning sleepiness	Week 2	11.1 (13.5)	8.7 (12.5)	10.4 (11.4)	12.5 (15.7)	11.9 (13.3)	12.3 (13.1)
	Week 4	17.4 (16.7)	14.7 (17.1)	15.5 (16.4)	17.4 (18.1)	17.0 (17.6)	16.2 (15.8)
Daytime alertness	Week 2	10.2 (14.7)	10.1 (14.8)	11.4 (10.4)	11.2 (15.2)	11.5 (12.6)	12.7 (17.0)
	Week 4	15.7 (17.9)	15.1 (19.5)	16.6 (14.9)	17.0 (19.4)	16.0 (15.9)	17.3 (17.9)
Daytime ability to function	Week 2	10.4 (15.2)	10.4 (13.6)	12.3 (10.0)	11.2 (15.0)	12.4 (14.0)	13.0 (15.9)
	Week 4	16.2 (17.7)	15.5 (20.0)	17.6 (14.5)	16.1 (19.2)	17.1 (16.6)	16.6 (17.3)

Data are least squares mean (standard error of the mean), unless otherwise specified.

[a]Zolpidem results for WASO, LPS, sWASO, and sLSO are from a separate analysis of covariance model that includes only subjects from the zolpidem and placebo treatment group.

ISI = Insomnia Severity Index; LPS = latency to persistent sleep; SD = standard deviation; sLSO = subjective latency to sleep onset; sTST = subjective TST; sWASO = subjective WASO; TST = total sleep time; VAS = visual analog scale; WASO = wake after sleep onset.

TABLE 3. TEAEs by Treatment Group

n (%)	Placebo, 0mg, n = 60	Daridorexant 5mg, n = 60	Daridorexant 10mg, n = 58	Daridorexant 25mg, n = 60	Daridorexant 50mg, n = 61	Zolpidem, 10mg, n = 60
Subjects with at least 1 TEAE	18 (30)	21 (35)	22 (38)	23 (38)	21 (34)	24 (40)
Subjects with at least 1 serious TEAE	0	0	2 (3.4)	0	1 (1.6)	0
Angioedema	0	0	0	0	1 (1.6)	0
Accident at work	0	0	1 (1.7)	0	0	0
Craniocerebral injury	0	0	1 (1.7)	0	0	0
Myocardial infarction	0	0	1 (1.7)	0	0	0
Subjects with at least 1 TEAE leading to treatment discontinuation	0	0	2 (3.4)	0	1 (1.6)	1 (1.7)
Angioedema	0	0	0	0	1 (1.6)	0
Anxiety	0	0	0	0	0	1 (1.7)
Arthralgia	0	0	1 (1.7)	0	0	0
Headache	0	0	1 (1.7)	0	0	0
Pain in extremity	0	0	1 (1.7)	0	0	0
Renal pain	0	0	1 (1.7)	0	0	0
Tooth infection	0	0	1 (1.7)	0	0	0
TEAE occurring in >1 subject in any group						
Abdominal pain upper	1 (1.7)	0	1 (1.7)	0	1 (1.6)	4 (6.7)
Alanine aminotransferase increased	0	0	0	2 (3.3)	1 (1.6)	0
Blood calcium decreased	2 (3.3)	0	0	0	0	0
Blood creatine phosphokinase increased	1 (1.7)	2 (3.3)	1 (1.7)	1 (1.7)	1 (1.6)	0
Diarrhea	2 (3.3)	1 (1.7)	0	3 (5.0)	0	1 (1.7)
Dizziness	1 (1.7)	1 (1.7)	2 (3.4)	0	0	4 (6.7)
Erythema	0	2 (3.3)	0	0	0	0
Fatigue	2 (3.3)	1 (1.7)	1 (1.7)	3 (5.0)	0	4 (6.7)
Gait disturbance	1 (1.7)	0	0	0	0	2 (3.3)
Gamma-glutamyltransferase increased	0	1 (1.7)	0	2 (3.3)	0	0
Headache	1 (1.7)	6 (10.0)	5 (8.6)	5 (8.3)	5 (8.2)	6 (10.0)
Nasopharyngitis	4 (6.7)	2 (3.3)	2 (3.4)	0	2 (3.3)	5 (8.3)
Nausea	0	0	1 (1.7)	2 (3.3)	1 (1.6)	4 (6.7)
Pruritus	0	0	0	0	2 (3.3)	0
Somnolence	3 (5.0)	3 (5.0)	3 (5.2)	4 (6.7)	4 (6.6)	3 (5.0)
TEAEs of special interest, after ISB adjudication						
Somnolence	0	0	1 (2)	1 (2)[a]	2 (3)	0
Hypersomnia	0	0	0	1 (2)[a]	0	0

[a]Adverse events occurred in the same subject.
ISB = independent safety board; TEAE = treatment-emergent adverse event.

Supplementary Table 1) and days 28 and 29 (see Fig 2, Table 2). Placebo-corrected LS mean estimates of change from baseline to days 1 and 2 in LPS were calculated (see Supplementary Table 2). TST increased from baseline on days 1 and 2 and showed a significant dose–response relationship ($p < 0.001$), also showing sustained effects at days 15 and 16 (see Supplementary Table 1) and days 28 and 29.

Subjective sleep parameters showed a dose–response relationship with daridorexant (see Fig 2, Table 2). A significant dose–response relationship at 4 weeks was observed for sWASO ($p = 0.045$), but the dose–response relationship was not significant for sLSO ($p = 0.107$). A significant dose-dependent increase in sTST was found with daridorexant ($p = 0.006$).

ISI scores did not show a dose-dependent relationship. The absolute change from baseline to day 30 was similar between placebo and daridorexant, and smaller than the zolpidem comparator (see Table 2).

VAS data were consistent with the sleep quality subjectively experienced by subjects in the zolpidem group (see Table 2). Sleep quality was judged to be better at week 4 than week 2 in all groups.

There were no differences in sleep parameters between male and female subjects (Supplementary Tables 3 and 4).

Safety

The incidence of treatment-emergent AEs was 35%, 38%, 38%, and 34% in subjects treated with 5, 10, 25, and 50mg daridorexant, respectively, compared with 30% in subjects on placebo, and 40% in the 10mg zolpidem-treated group (Table 3). No relationship to the daridorexant dose was seen in the overall incidence of AEs, or the incidence of any specific AE. The most frequent AEs in subjects treated with daridorexant were headache (up to 10%), somnolence (up to 7%), diarrhea (up to 5%), and fatigue (up to 5%). At least 1 SAE was reported for 3 subjects, but none was considered to be related to treatment by the investigator. One subject on daridorexant 50mg had angioedema. In the 10mg daridorexant group, 1 subject reported myocardial infarction, and another had 2 SAEs: accident at work and craniocerebral injury. Treatment-emergent AEs leading to premature discontinuation of double-blind treatment were reported for 4 subjects: tooth infection (1 subject on 10mg daridorexant); arthralgia, headache, pain in extremity, and renal pain (all in 1 subject on 10mg daridorexant); angioedema (1 subject on 50mg daridorexant); and anxiety (1 subject on 10mg zolpidem). There were no deaths.

VASs on morning sleepiness, daytime alertness, and daytime ability to function all showed nonsignificant increases in a dose-dependent manner at higher doses of daridorexant compared with placebo at week 2, which was not sustained at week 4 (see Table 2). This pattern was also true for zolpidem compared with placebo. The DSST, KSS, and SDS scores showed no dose-dependent effect (Supplementary Table 5).

Independently adjudicated AESIs were reported in 4 subjects (1 at 10mg, 1 at 25mg, 2 at 50mg). They were of mild or moderate intensity and assigned to the category "narcolepsy," subcategory "excessive daytime sleepiness event." All AESIs were considered by the ISB to be probably out of the scope of the narcolepsy spectrum, based on available clinical data (eg, absence of repetitive, irresistible, and refreshing naps of short duration throughout the day, and absence of cataplexy symptoms). There was no report of suicidal ideation or behavior, or self-injurious behavior.

No drug-related effects were found on blood pressure, body weight, ECG, or clinical laboratory assessments. There was no evidence of treatment-emergent AEs suggesting drug abuse, rebound insomnia, or drug withdrawal syndrome.

Discussion

This phase 2 study of a new DORA, daridorexant, demonstrated an objectively assessed, significant improvement compared with placebo in sleep induction and maintenance with a significant dose–response relationship in subjects with insomnia disorder. Subjective sleep parameters supported the dose–response relationship. The study was consistent with the safety and tolerability profile of daridorexant shown in previous studies.[12–14]

Changes from baseline in objective efficacy measurements (LPS and WASO) observed on days 1 and 2 were sustained on days 15 and 16 and days 28 and 29. Subjective sleep parameters (sWASO and sTST) supported the primary findings. Consistent with previous studies, zolpidem 10mg, which was included as an active control, improved sleep latency parameters and had no significant effect on WASO.[26]

Daridorexant has shown a profile in which PK and PD are in accordance, that is, for a certain dose the duration of effects is explained by its PK profile (demonstrated by the dose–response relationship in the reduction of WASO from baseline), also due to the absence of active metabolites. Conversely, a difference in half-life of several hours can have an important impact on the propensity to elicit next-morning residual drug effects, emphasized in the current study by the absence of such effects up to and including the highest dose.

The overall safety and tolerability of daridorexant were favorable. No clinically relevant treatment-related SAEs were reported. Independently adjudicated AESIs were reported in 4 subjects, but there was no significant concern relating to AEs linked to narcolepsylike symptoms

and no evidence of suicidal ideation or behavior, or drug abuse.

One of the main concerns with current insomnia products is the potential for residual next-morning effects. The assessment of morning sleepiness showed no difference between any dose of daridorexant and placebo in terms of sleepiness the following day. This is assumed to be related to the short half-life of daridorexant, as shown in phase 1 clinical trials in healthy subjects.[11,14] The relatively short half-life of daridorexant may also result in fewer residual effects. In addition, daridorexant, in common with all DORAs, is designed to improve the quality of sleep, so an absence of next-morning residual effects would not be unexpected and would support the data generated showing objective improvement.

Other concerns are the presence of withdrawal symptoms following cessation of treatment[5] and the development of tolerance/tachyphylaxis. Our study included a run-out period to assess potential for rebound or occurrence of drug withdrawal syndrome, and no such effects were observed with daridorexant on subjective or objective parameters during the withdrawal period. Although tolerance is an important consideration concerning sleep medications, the current data from this phase 2 study are limited to definitively conclude potential tolerance/tachyphylaxis. Long-term phase 3 clinical trials (ClinicalTrial.gov: NCT03545191, NCT03575104, NCT03679884) will further explore any potential tolerance/tachyphylaxis to daridorexant.

Limitations

No significant effects were observed on ISI or VAS sleep quality. The dose–response relationship was not significant for sLSO, which was also the case in the zolpidem group—an approved treatment for its effect on sleep induction. Such limitation on interpretation of subjective parameters is inherent in a relatively small phase 2 study, with the study neither designed nor powered to address questions of clinically significant improvement, but to determine the dose–response and identify which dose(s) should be pursued in further development. However, our study was powered to and did show promising results in objective parameters, which have been demonstrated to provide valuable information on medical comorbidities of insomnia disorder such as activation of the stress system, cardiovascular and metabolic disorders, neurocognitive impairment, and mortality.[27] The study was powered based on the most sensitive parameters, those with less variability: the objective PSG parameters. Insomnia with objective short sleep duration is the most biologically severe phenotype of the disorder.[27] Daridorexant showed objective improvement in sleep onset and maintenance, suggesting that it could be an alternative therapeutic option to treat insomnia disorder with short sleep duration and associated comorbidities. The 4-week duration does not allow for assessment of efficacy and safety of long-term use. This study did not include elderly subjects nor subjects with comorbid insomnia disorders.[28,29] The effects of daridorexant in elderly subjects were investigated in a parallel phase 2 study (Clinicaltrials.gov NCT03575104). It will also be important to assess whether improvement in sleep is associated with improvement of next-day performance, which this study was not designed to address.

In conclusion, daridorexant induced a dose–response effect on sleep onset and sleep maintenance in subjects with insomnia, without dose-limiting safety issues in the dose range studied. The sustained robust efficacy observed in this phase 2 study should be confirmed in a larger and broader population of subjects with insomnia disorder, for a longer study period. These results suggest that daridorexant may represent an alternative therapeutic option to treat insomnia disorder.

Acknowledgment

This study was sponsored by Actelion Pharmaceuticals. Study sponsorship was transferred to Idorsia Pharmaceuticals in July 2018. The sponsor (initially Actelion Pharmaceuticals, then Idorsia Pharmaceuticals) participated in the design and conduct of the study; and collection, management, analysis, and interpretation of the data. All authors had access to the full dataset and analysis. All authors reviewed the data and analysis, formulated their own interpretation of the data, and wrote the conclusions. All conclusions within the article were agreed upon unanimously by all authors.

We thank all subjects, study investigators, study staff, and nursing teams for their participation in this research; and Dr L. Rettig of nspm for providing editorial and logistical support in the final preparation of the manuscript, which was funded by Idorsia Pharmaceuticals.

Author Contributions

Y.D., G.Z., D.S.K., and J.H. contributed to the conception and design of the study; all authors contributed to the acquisition and analysis of data; all authors contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

Y.D. reports board membership, consultancy, and lecture activity with Idorsia. G.Z. is an employee of Clinilabs Drug Development Corporation, a company that has received grants from Idorsia. I.F. has consulted for Idorsia

and has conducted studies for Actelion and Idorsia. D.M. has served as clinical trial investigator for Actelion and Idorsia. D.S.K. and S.P. are current employees of Idorsia and were employees of Actelion at the time of conduct of the study. J.H. has served as clinical trial investigator for Idorsia.

References

1. Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder. Nat Rev Dis Primers 2015;1:15026.
2. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165:125–133.
3. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26:675–700.
4. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4:487–504.
5. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13:307–349.
6. Neubauer DN, Pandi-Perumal SR, Spence DW, et al. Pharmacotherapy of insomnia. J Cent Nerv Syst Dis 2018;10:1179573518770672.
7. Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: a systematic review and meta-analysis. Sleep Med Rev 2017;35:1–7.
8. Belsomra (suvorexant) [package insert]. Kenilworth, NJ: Merck Sharp & Dohme, 2018.
9. Herring WJ, Connor KM, Ivgy-May N, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2016;79:136–148.
10. Citrome L. Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014;68:1429–1441.
11. Treiber A, de Kanter R, Roch C, et al. The use of physiology-based pharmacokinetic and pharmacodynamic modeling in the discovery of the dual orexin receptor antagonist ACT-541468. J Pharmacol Exp Ther 2017;362:489–503.
12. Muehlan C, Brooks S, Zuiker R, et al. Multiple-ascending-dose study of ACT-541468, a novel dual orexin receptor antagonist: characterization of its multiple-dose pharmacokinetics, pharmacodynamics, safety, and tolerability. Sleep 2018;41(suppl 1):A3-A.
13. Muehlan C, Brooks S, Zuiker R, et al. Night-time administration of ACT-541468, a novel dual orexin receptor antagonist: characterization of its pharmacokinetics, next-day residual effects, safety, and tolerability. Sleep 2018;41(suppl 1):A3-A.
14. Muehlan C, Heuberger J, Juif PE, et al. Accelerated development of the dual orexin receptor antagonist ACT-541468: integration of a microtracer in a first-in-human study. Clin Pharmacol Ther 2018;104: 1022–1029.
15. Diagnostic and statistical manual of mental disorders. *5th ed.* Arlington, VA: American Psychiatric Association, 2013.
16. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
17. Buysse DJ, Ancoli-Israel S, Edinger JD, et al. Recommendations for a standard research assessment of insomnia. Sleep 2006;29: 1155–1173.
18. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.
19. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Int J Neurosci 1990;52:29–37.
20. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11(suppl 3):89–95.
21. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266–1277.
22. Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. J Affect Disord 1990;19:53–61.
23. Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat 2006;16:639–656.
24. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 2005; 61:738–748.
25. Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Stat Med 2014;33:1646–1661.
26. Erman MK, Zammit G, Rubens R, et al. A polysomnographic placebo-controlled evaluation of the efficacy and safety of eszopiclone relative to placebo and zolpidem in the treatment of primary insomnia. J Clin Sleep Med 2008;4:229–234.
27. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. Sleep Med Rev 2013;17:241–254.
28. Dauvilliers Y. Insomnia in patients with neurodegenerative conditions. Sleep Med 2007;8(Suppl 4):S27–S34
29. Mayer G, Jennum P, Riemann D, Dauvilliers Y. Insomnia in central neurologic diseases–occurrence and management. Sleep Med Rev 2011;15(6):369–378.