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ORIGINAL ARTICLE

Abuse potential assessment of the new dual orexin receptor antagonist daridorexant in recreational sedative drug users as compared to suvorexant and zolpidem

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Abstract

Study Objectives: Abuse potential properties have been reported for the dual orexin receptor antagonists (DORAs) suvorexant and lemborexant. Daridorexant is a new DORA currently in late-stage clinical development. This randomized, double-blind, double-dummy, placebo- and active-controlled six-period crossover study assessed its abuse potential in healthy recreational sedative drug users ($n = 63$).

Methods: In each study period, a single, oral, morning dose of either daridorexant (50, 100, and 150 mg), placebo, or active control, i.e. suvorexant (150 mg) or zolpidem (30 mg), was administered. Primary pharmacodynamic (PD) endpoint was the E_{max} of the drug-liking visual analog scale (VAS) assessed over 24 h. Several secondary subjective and objective PD endpoints were also assessed.

Results: Study validity was confirmed based on drug-liking of suvorexant and zolpidem greater than placebo applying a predefined 15-point validity margin ($p < 0.0001$). Drug-liking VAS E_{max} (mean; 95% confidence interval) of daridorexant at 50 mg (73.2; 69.0–77.5) was significantly lower compared to suvorexant (80.7; 77.0–84.5) and zolpidem (79.9; 76.2–83.5) ($p < 0.001$), but similar at 100 mg (79.1; 75.0–83.3) and 150 mg (81.3; 77.7, 84.8). Such dose-related patterns were also observed for most secondary endpoints. At each daridorexant dose, Drug-liking VAS scores were greater than placebo. Both control drugs and daridorexant were safe and the pharmacokinetics of daridorexant was consistent with earlier trials indicating quick absorption and elimination.

Conclusions: In this large, valid human abuse potential study, daridorexant showed dose-related drug-liking among recreational sedative drug users with lower effects at the highest phase-3 dose, and similar effects at higher doses compared to supratherapeutic doses of suvorexant and zolpidem.

Clinical Trial Registration: Study to Evaluate the Abuse Potential of ACT-541468 in Healthy Recreational Drug Users, https://www.clinicaltrials.gov/ct2/show/NCT03657355?term=ACT-541468&draw=3&rank=18, NCT03657355.

Statement of Significance

The high prevalence of insomnia and shortcomings of existing therapies highlight a major unmet need for safe, effective, and well-tolerated pharmacological treatments of insomnia. Daridorexant is a new dual orexin receptor antagonist (DORA) with profound, dose-dependent sleep-promoting effects and lack of next-morning residual effects in adult and elderly insomnia patients. This large, valid human abuse potential study indicates lower abuse potential of daridorexant at the highest phase-3 dose, and similar effects at higher doses compared to supratherapeutic doses of the control drugs suvorexant and zolpidem in recreational sedative drug users. These results together with other preclinical and clinical data regarding abuse and dependence potential are relevant for regulatory decision-making and cross-study comparisons with other DORAs including suvorexant and lemborexant.

Key words: abuse potential; ACT-541468; daridorexant; drug-liking; dual orexin receptor antagonist; recreational drug user; sleep; suvorexant; visual analog scale; zolpidem

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Introduction

Insomnia is defined as dissatisfaction with sleep quantity or quality including difficulty initiating, maintaining, or returning to sleep and is associated with daytime functional impairment [1]. Approximately 30% of the general population are affected by insomnia-related symptoms and the prevalence of insomnia in the general population as defined by guideline-based diagnostic criteria is approximately 10% [2, 3]. Hence, insomnia represents a major public health issue which is further underscored by the occurrence of several relevant comorbidities in particular psychiatric conditions such as anxiety, depression, and suicidal behavior [4–6].

According to US and EU guidance, cognitive behavioral therapy is recommended as first-line treatment of chronic insomnia in adults and, if unsuccessful, pharmacological intervention should be considered [7, 8]. Here, benzodiazepines (e.g. temazepam) and non-benzodiazepine receptor agonists (non-BZRAs) (e.g. zolpidem, (es)zopiclone) are still most commonly used and generally considered effective in the short-term treatment of insomnia [9]. However, benzodiazepines have traditionally been associated with misuse, tolerance development, and the occurrence of withdrawal effects following cessation of long-term treatment triggering dependence potential [10]. Their utility is further limited due to numerous relevant adverse effects, e.g. next-morning residual effects, rebound insomnia, cognitive impairment, confusion, gait disturbances, and fall-related injuries [10–12]. By contrast, non-BZRAs have a lower dependence potential liability and their safety and tolerability profile is generally in favor of benzodiazepines although relevant adverse effects may occur mainly in context of long-term use (e.g. dementia, hallucinations, and delirium) [12, 13].

The high prevalence of insomnia together with the shortcomings of existing therapies highlight a major unmet clinical need for safe, effective, and well-tolerated pharmacological treatments of insomnia or related symptoms. To this end, the orexin receptor has evolved as promising druggable target for development of sleep-promoting agents with a presumably more favorable benefit/risk profile [10, 14, 15]. In contrast to benzodiazepines or non-BZRAs, dual orexin receptor antagonists (DORAs) appear essentially devoid of withdrawal effects as reflected in the US labeling information of the approved DORAs suvorexant and lemborexant [16, 17]. Interestingly, DORAs have also been shown to attenuate cocaine-mediated dopamine release and impulsive behavior in rodent models, which is conceivable as hypothalamic orexin peptides are involved in reward processing [18, 19]. Another differentiating aspect of DORAs concerns their absence of respiratory depressant effects even in at-risk patients with obstructive sleep apnea [20–22] or chronic obstructive pulmonary disease [23, 24]. By contrast, respiratory depression is a well-established safety risk of benzodiazepines particularly in combination with opioids [25].

For drugs with central nervous system (CNS) activity, human abuse potential (HAP) studies are often requested by the Food and Drug Administration (FDA) as part of the drug approval process in the United States. Such HAP studies assess subjective drug-liking and other endpoints of relevance for the abuse potential evaluation following administration of therapeutic and supratherapeutic single doses with reference to at least one positive control drug of the same or similar class. HAP study data as well as other relevant preclinical and clinical data form the basis for a comprehensive abuse and dependence potential evaluation that drives the decision about appropriate regulatory scheduling of medications in the United States [26].

As the first DORA, suvorexant was approved in 2014 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Its potential for abuse has been evaluated in a dedicated HAP study, in which suvorexant exhibited drug-liking effects greater than placebo and similar to the positive control drug zolpidem in recreational drug users [27]. It has been classified as schedule IV compound under the Controlled Substances Act and the prescribing information contains a warning regarding its abuse potential [16].

More recently, lemborexant has been approved as the second DORA for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance [28]. It has also been shown to trigger drug-liking effects greater than placebo and similar to the positive control drugs suvorexant and zolpidem in recreational drug users [28, 29].

Daridorexant (ACT-541468) is a new, selective, and potent competitive antagonist of the orexin-1 and orexin-2 receptor currently in late-stage clinical development. In a panel screen of more than 120 established central and peripheral pharmacological targets, it has been shown to be highly selective for the orexin-1 and orexin-2 receptor suggesting lack of relevant off-target binding to receptors mediating abuse-related effects [30]. In healthy participants, favorable pharmacokinetic (PK) and pharmacodynamic (PD) properties including quick absorption (i.e. time to maximum plasma concentration [t_{max}] ~1 h) and elimination (i.e. terminal elimination half-life [$t_{1/2}$] approximately 8 h) have been determined leading to absence of next-morning residual effects [31–33]. In phase-2, daridorexant demonstrated dose-dependent efficacy indicated by a significant reduction of the objective sleep parameters wake after sleep onset and latency to persistent sleep in adult [34] and elderly [35] patients with insomnia. Notably, following treatment cessation, no withdrawal effects were detected based on the Benzodiazepine Withdrawal Symptom Questionnaire [36] after a 30-day treatment period [34].

Here, we report on results from the HAP study with daridorexant comparing its drug-liking and other abuse-related parameters with those of placebo and two positive control drugs, namely suvorexant and zolpidem.

Methods

This was a randomized, double-blind, double-dummy, placebo- and active-controlled HAP study in recreational sedative drug users. The study was registered on ClinicalTrials.gov (NCT03657355) and conducted in compliance with the Declaration of Helsinki principles, International Council on Harmonization Good Clinical Practice guidelines, and US FDA regulations. It was approved by the Midlands Independent Review Board (Kansas City, MO, USA), and all study participants provided written informed consent prior to any study procedures.

The study consisted of a qualification and core phase (Supplementary Figure S1). The goal of the qualification phase was primarily to identify those participants who could discriminate drug-liking effects of each control drug from placebo based on visual analog scale (VAS) data as required for eligibility in the subsequent core phase of the study.

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Study population

Healthy male and female participants aged 18–55 years and with a body mass index of 18.0–33.0 kg/m^2 were enrolled. Their health status was determined based on physical examination, medical history, and assessments of vital sign, clinical laboratory, and 12-lead electrocardiogram (ECG) data.

Each participant had to be a recreational user of sedatives as defined by at least 10 lifetime occasions of using CNS depressants (e.g. benzodiazepines, zolpidem, eszopiclone, gamma-hydroxybutyrate, barbiturates) for recreational purposes and at least one occasion within 12 weeks prior screening. Women of childbearing potential were required to use a highly effective method of contraception, i.e. with a failure rate of <1% per year.

Key study-specific exclusion criteria included a positive urine drug screen at admittance (except for cannabinoids) and a history or presence of substance or alcohol dependence, any treatment of substance- or alcohol-related disorders, or prior participation in a substance or alcohol dependence rehabilitation program. Moreover, heavy smokers were excluded as defined by a consumption of >20 cigarettes per day (or equivalent nicotine exposure) in the month prior to the screening visit. Consumption of nicotine was prohibited from at least 1 h prior until 5 h post each dosing. Concomitant medications were prohibited during the study unless required for treatment of adverse events (AEs) or contraception.

Study drugs and dose selection

The doses of daridorexant were selected to include 50 mg as highest phase-3 dose and 100 and 150 mg as supratherapeutic doses exceeding the highest tentative therapeutic dose by 2–3 times in compliance with FDA guidance [26].

The positive control drug should be approved by FDA, pharmacologically similar to the test drug, and scheduled under the Controlled Substances Act. Therefore, suvorexant was selected as a control drug representing the first DORA approved for treatment of insomnia in the United States and assigned to schedule IV. A supratherapeutic dose of 150 mg (i.e. 7.5–15-fold the therapeutic dose range) was selected which triggered positive psychoactive effects distinguishable from placebo and indicative of abuse potential in an earlier HAP study [27].

As a second control drug, the selective non-BZRA zolpidem was selected, as it is approved for short-term treatment of insomnia in the United States and has also been assigned to schedule IV. Zolpidem has been used as control drug in several earlier HAP studies and its drug-liking and perception-altering effects at the selected supratherapeutic dose of 30 mg (i.e. 3–6-fold the therapeutic dose range) are well established [27, 37].

Daridorexant was supplied as tablets at a dose strength of 50 mg. In addition, a matching placebo tablet was supplied. In each period of the core phase, each participant orally received a total of three tablets, i.e. an appropriate number of daridorexant or matching placebo tablets depending on the treatment assigned.

Suvorexant and zolpidem were also supplied as tablets at a dose strength of 15 and 10 mg, respectively. These tablets were over-encapsulated to maintain blinding and an over-capsule was prepared for each control drug containing two tablets of suvorexant or one tablet of zolpidem. In addition, a methylcellulose-filled over-capsule was used as matching placebo. In each period of the qualification and core phase each participant orally received a total of five over-capsules, i.e. an appropriate number of over-capsules containing suvorexant, zolpidem, or placebo depending on the treatment assigned.

Qualification phase

Participants who met eligibility requirements at screening underwent a randomized, double-blind, three-period qualification phase.

In each period, participants received a single oral dose of either 150 mg suvorexant, 30 mg zolpidem, or placebo in the morning under fasted conditions (i.e. from 10 h prior until 4 h after each dosing). Repeated drug-liking and other computerized PD assessments were performed up to 24 h post each dosing. The washout period in between each dosing lasted for at least 72 h. Participants remained domiciled for the entire duration of the qualification phase, i.e. from the day prior first dosing until at least 24 h post last dosing.

Eligibility for the core phase was primarily determined based on Drug-liking VAS E_{max} data indicating (1) the ability to distinguish orally administered suvorexant and zolpidem from placebo (i.e. ≥65 points in absolute response to suvorexant and zolpidem and ≥15 points higher in response to suvorexant and zolpidem as compared to placebo) and (2) a neutral placebo response (i.e. 40–60 points in response to placebo). In addition, each participant had to demonstrate an acceptable tolerability of the study drugs and a general behavior suggesting that the participant could successfully complete the required study assessments.

Noneligible participants were released from the study site ≥24 h after last dosing and underwent an end-of-study visit ≥72 h after last dosing. Eligible participants remained at the study site to proceed with the core phase after a washout period that lasted ≥72 h (i.e. from last dosing in the qualification phase to first dosing in the core phase).

Core phase

The core phase of this study had a six-period crossover design. In each period, a single, oral dose of either daridorexant (50, 100, and 150 mg), suvorexant (150 mg), zolpidem (30 mg), or placebo was administered in the morning. The treatment sequence was randomized applying a 6 × 6 Williams square design to mitigate potential first-order carry-over effects.

Each dosing occurred in the morning under fasted conditions as described for the qualification phase followed by computerized PD assessments up to 24 h post each dosing and applying a washout period of ≥72 h. Participants remained domiciled for the entire duration of the core phase, i.e. until at least 24 h after last dosing and returned for an end-of-study visit ≥72 h after last dosing.

PD assessments

The primary PD endpoint was the E_{max} of the bipolar "at-the-moment" Drug-liking VAS ranging from 0 (=maximum disliking) to 100 points (=maximum liking) with a score of 50 representing a neutral response. The Drug-liking VAS was assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h post dosing.

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Several secondary PD endpoints were collected (Supplementary Table S1). The balance of positive and negative effects was assessed based on bipolar (Overall Drug-liking and Take Drug Again VAS) and unipolar scales (Good effects, Bad Effects, and Feeling High VAS). Perceptual/psychedelic and any effects were assessed based on the unipolar Bowdle VAS [38] and Any Effects VAS, respectively. Sedative effects were measured based on the bipolar Alertness/Drowsiness VAS and the Observer's Assessment of Alertness/Sedation (OAA/S) (composite and sum scores) [39]. Each of these secondary PD endpoints was determined at the same time points as the primary endpoint except for the Overall Drug-liking and Take Drug Again VAS, which were determined at 12 and 24 h only to assess the overall extent of drug-liking and willingness to take the study drug again from dosing until time of assessment.

In addition, the drug similarity VAS was determined at 12 h post each dosing to assess how similar the perceived effects were compared to drugs or drug classes previously used by the study participants for recreational purposes.

Lastly, objective cognitive function tests were also applied at 0.5, 1, 2, 4, and 8 h post dosing using the validated Cambridge Cognition cognitive assessment software [40]. These included the (1) Reaction Time Task (RTI) to assess psychomotor performance (based on five-choice reaction time and error score), (2) Paired Associate Learning (PAL) to assess episodic memory (based on total attempts and first attempt memory score), and (3) Rapid Visual Information Processing (RVP) to assess sustained attention (based on target sensitivity and median response latency). To mitigate potential practice effects, training sessions were conducted prior to the qualification phase and the ability to reliably complete each of these cognitive function tests in the qualification phase was required for admission into the core phase.

PK assessments

Blood samples were taken predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 h post dosing. Plasma was stored at –70°C and protected from light. Concentrations of daridorexant were determined using a validated liquid chromatography–tandem mass spectrometry assay with a lower limit of quantification of 0.5 ng/mL [33]. The method was linear in the concentration range from 0.5 to 1600 ng/mL. Inter-batch precision (%CV) was ≤6.7% and accuracy ranged from 94.2% to 106.6%. PK parameters of daridorexant were determined by noncompartmental analysis using Professional WinNonlin 8.0 software (Pharsight Corp., Mountain View, CA).

Safety assessments

Safety and tolerability were monitored based on repeated assessments of AE, vital sign, clinical laboratory, 12-lead ECG, and Columbia-Suicide Severity Rating Scale (C-SSRS) data until 24 h post dosing and at the end-of-study visit.

Statistical hypotheses

The primary PD analysis was based on evaluating the treatment differences of the mean (μ) Drug-liking VAS E_{max} during the core phase with respect to the following questions (Q), contrasts, and null hypotheses (H_0):

Q1. Did each positive control drug produce mean drug-liking responses greater than placebo?

H_0: μ (control drug) – μ (placebo) ≤ δ_1 versus H_a: μ (control drug) – μ (placebo) > δ_1

A minimum of 15 points greater drug-liking than on placebo was required (i.e. $\delta_1 \geq 15$) to claim study validity for each control drug.

Q2. Did daridorexant produce mean drug-liking responses smaller than the positive control drugs?

H_0: μ (control drug) – μ (daridorexant) ≤ δ_2 versus H_a: μ (control drug) – μ (daridorexant) > δ_2

Responses to daridorexant were considered smaller than those to suvorexant and zolpidem if significantly lower drug-liking could be determined (i.e. $\delta_2 = 0$).

Q3. Did daridorexant produce mean drug-liking responses similar to placebo?

H_0: μ (daridorexant) – μ (placebo) ≥ δ_3 versus H_a: μ (daridorexant) – μ (placebo) < δ_3.

Similar drug-liking effects of daridorexant compared to placebo required a difference of 11 points or less was required (i.e. $\delta_3 \leq 11$) [41].

A hierarchical testing approach was applied and hence no multiplicity adjustment was applied [26]. The analyses of secondary PD endpoints followed the same principles described for the primary analysis except that no formal validity testing was required.

Sample size estimation

The sample size was selected to ensure statistical differentiation between the positive control drugs and placebo with respect to the primary PD endpoint. Based on previous HAP studies, a true mean difference from placebo in Drug-liking VAS E_{max} of ≥24.3 points (SD ≤21.7) and ≥22.5 points (SD ≤20) was assumed for zolpidem and suvorexant, respectively [27, 37, 42].

A minimum sample size of 60 participants with evaluable PD data from each study period was estimated to achieve at least 80% power in detecting a mean difference in Drug-liking VAS E_{max} between zolpidem or suvorexant and placebo of ≥15 points (one-sided test; alpha 0.05).

Statistical analyses

The Shapiro–Wilk Normality test was applied to evaluate whether the data were normally distributed. If the data were normally distributed, peak scores (E_{max} and/or E_{min}, as applicable) of each PD endpoint were analyzed using a linear mixed-effects model, which included period, sequence, and treatment as fixed effects, and subject nested within sequence as random effect. For all contrasts, the point estimates, associated 95% confidence intervals (CIs), and *p* values were derived from the mixed-effects model.

In case of normal distribution, treatment differences were analyzed by paired *t*-test and provided as mean and standard error, while in case of nonnormal distribution the nonparametric sign test was used and data were provided as medians of paired difference together with the interquartile range (Q1–Q3).

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Statistical tests for primary hypotheses were one sided as specified above (alpha 0.05). For secondary endpoints, contrasts between positive control and placebo, and between daridorexant and positive controls were one sided (alpha 0.05), while contrasts between daridorexant and placebo were two sided (alpha 0.10) [26].

The PD analysis included participants who received at least one dose of study drug and who had at least one Drug-liking VAS assessment within ±2 h of t_{max} of each treatment. Effect size estimates (Cohen's *D*) were derived based on estimates for within-subject standard deviation from a mixed-effects model [43].

The PK/PD relationship was evaluated by linear regression analysis of individual Drug-liking VAS E_{max} and C_{max} of daridorexant obtained at all doses.

Demographics, baseline characteristics, PK, and safety data were summarized descriptively.

Results

Participant disposition and demographics

In the qualification phase, 225 participants were randomized of which 219 participants were exposed to any study drug resulting in 72 eligible participants. Main reasons for noneligibility were inappropriate responses to at least one control drug (i.e. Drug-liking VAS E_{max} <65) or placebo (i.e. Drug-liking VAS E_{max} >60). In the core phase, 71 of the identified eligible participants were exposed and 63 participants completed all 6 study periods per protocol. These were hence included in the PD data analysis, while eight participants were discontinued due to AEs (n = 1), withdrawal of consent (n = 3), or for other reasons (n = 4).

There were 54 male (76.1%) and 17 female (23.9%) participants with a mean age (SD) of 31.5 (7.60) years. Most participants were Black or African American (n = 54; 76.1%) followed by White (n = 15; 21.1%) and participants of another ethnicity (n = 2; 2.8%). There were no marked demographic differences between exposed participants who passed versus those who did not pass the qualification phase in terms of age, weight, height, or BMI. The proportion of female participants was higher among those who passed (n = 54/17) versus those who did not pass the qualification phase (n = 125/23 male/female participants).

Per protocol, all study participants had recreational experience with sedative drugs and most of them also had experience with cannabinoids (94.4%), opioids (73.2%), and stimulants (70.4%), while less participants had previously used hallucinogens (46.5%) or anesthetics (11.3%).

Primary PD results

The mean drug-liking over time plot indicates a similar time to peak effect of approximately 1.5–2 h post dosing for all doses of daridorexant as well as for the control drugs suvorexant and zolpidem (Figure 1).

The primary endpoint analysis revealed Drug-liking VAS E_{max} scores (mean; 95% CI) of suvorexant (80.7; 77.0–84.5) and zolpidem (79.9; 76.2–83.5) that were significantly higher compared to placebo (55.1; 52.0–58.1). The lower bound of the 95% CI of the mean difference from placebo exceeded the predefined 15-point validity margin for both suvorexant (25.7; 21.4–29.9) and zolpidem (24.8; 20.5–29.0) thereby confirming study validity with respect to both control drugs (Table 1).

The Drug-liking VAS E_{max} of daridorexant increased from 73.2 (69.0–77.5) at 50 mg to 79.1 (75.0–83.3) and 81.3 (77.7–84.8) at 100 and 150 mg, respectively (Figure 2).

At the dose of 50 mg, daridorexant showed significantly less drug-liking compared to both suvorexant and zolpidem indicated by mean differences (95% CI) of 7.5 (3.4–11.6) and 6.6 (2.7–10.5), respectively. No significant differences compared to both control drugs were determined at the doses of 100 and 150 mg daridorexant (Table 1). Equivalence of Drug-liking VAS

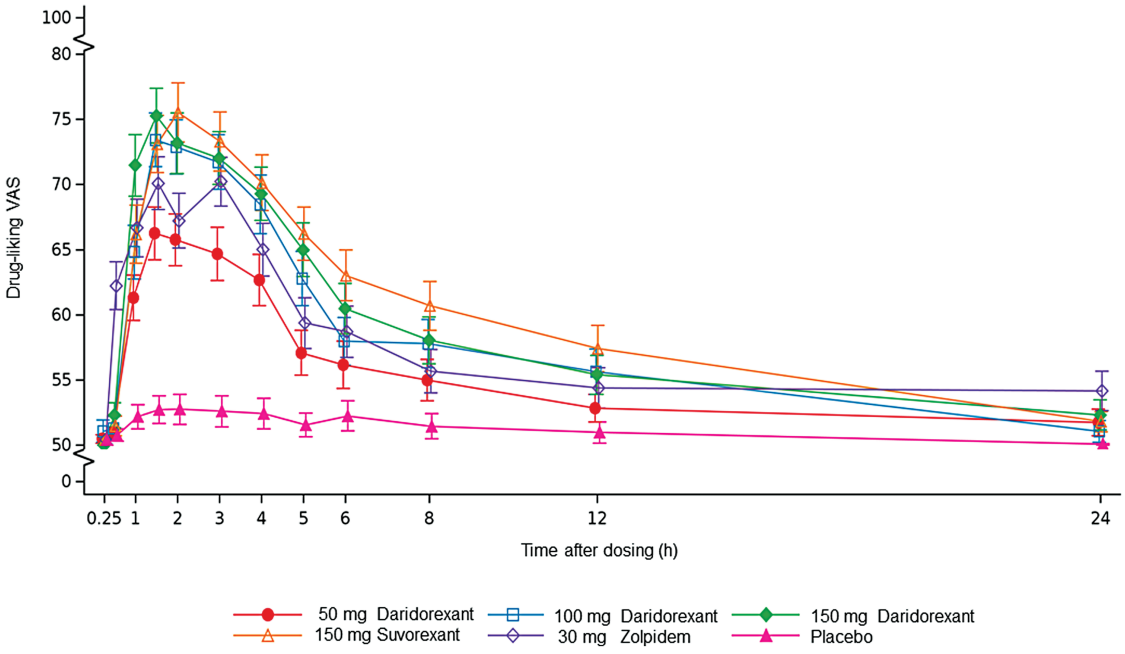


Figure 1. Mean Drug-Liking VAS over time and by treatment. Data are displayed as arithmetic mean and standard error. The y-axis has been cropped for better visibility, as there were no data points below 50 points (i.e. indicative of disliking).

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Table 1. Comparisons of Drug-liking VAS E_{max} between treatments

	Mean difference (95% CI)	P
Study validity: control drugs vs. placebo		
Suvorexant (150 mg)—placebo[b]	25.7 (21.4 to 29.9)	<0.0001*
Zolpidem (30 mg)—placebo[b]	24.8 (20.5 to 29.0)	<0.0001*
Relative abuse potential: control vs. test drug		
Suvorexant (150 mg)—daridorexant (50 mg)[a]	7.5 (3.4 to 11.6)	0.0003*
Suvorexant (150 mg)—daridorexant (100 mg)[b]	1.6 (−1.5 to 4.6)	0.1958
Suvorexant (150 mg)—daridorexant (150 mg)[a]	−0.6 (−3.1 to 2.0)	0.6658
Zolpidem (30 mg)—daridorexant (50 mg)[a]	6.6 (2.7 to 10.5)	0.0007*
Zolpidem (30 mg)—daridorexant (100 mg)[b]	0.7 (−3.2 to 4.6)	0.5000
Zolpidem (30 mg)—daridorexant (150 mg)[b]	−1.4 (−5.2 to 2.4)	0.6583
Absolute abuse potential: test drug vs. placebo		
Daridorexant (50 mg)—placebo[b]	18.2 (13.8 to 22.6)	n.a.*
Daridorexant (100 mg)—placebo[a]	24.1 (19.2 to 29.0)	n.a.*
Daridorexant (150 mg)—placebo[a]	26.2 (22.1 to 30.3)	n.a.*

Data are displayed as mean differences (95% CI) between treatments. Study hypotheses were one sided (alpha 0.05). Normality testing of residuals from the mixed-effect model was done by the Shapiro–Wilk W test with a p-value ≥0.05 indicating a normal distribution. To assess differences between two treatments, the paired t-test ([a]) or sign test ([b]) was used in case of normal or nonnormal data distribution, respectively. *A hierarchical testing approach was applied as required per FDA guidance and statistical significance was to be achieved at each dose of daridorexant regarding relative abuse potential in order to proceed with the absolute abuse potential assessment. As lower relative abuse potential of daridorexant compared to the control drugs was only determined for the dose of 50 mg, a formal statistical analysis of the absolute abuse potential was not applicable. n.a., not applicable.

E_{max} to placebo was not determined for any dose of daridorexant (Table 1).

Secondary PD results

Treatment comparisons of secondary PD results are summarized in Table 2. Mean subjective PD VAS data by active treatment are graphically displayed in a radar chart (Figure 3) and Drug similarity VAS data are shown in Figure 4.

Balance of effects Suvorexant, zolpidem, and all doses of daridorexant significantly differentiated from placebo with respect to both Overall Drug-liking and Take Drug Again VAS. Significantly lower Overall Drug-liking was determined for the dose of 50 mg daridorexant compared to both control drugs, while Take Drug Again VAS was lower only in comparison to suvorexant. At the doses of 100 and 150 mg daridorexant, no significant differences from control drugs were determined.

Results from the unipolar Good Effects and Feeling High VAS scales were consistent with the Overall Drug-liking and Take Drug Again VAS data. Suvorexant, zolpidem, and all doses of daridorexant significantly differentiated from placebo with respect to both scales. Daridorexant showed lower scores compared to both control drugs at the dose of 50 mg with respect to both scales. For the Feeling High VAS, this was also applicable at the dose of 100 mg daridorexant in comparison to zolpidem.

Treatment differences for the Bad Effects VAS are not reported given the low magnitude of responses on this measure (i.e. median E_{max} of 0.0 for all treatments).

Perceptual/psychedelic and any effects Suvorexant, zolpidem, and all doses of daridorexant significantly differentiated from placebo with respect to the Bowdle VAS assessing perceptual effects. Daridorexant showed significantly lower scores (i.e. fewer alterations of internal and external perception) compared to zolpidem at all doses and compared to suvorexant at doses of 50 and 100 mg.

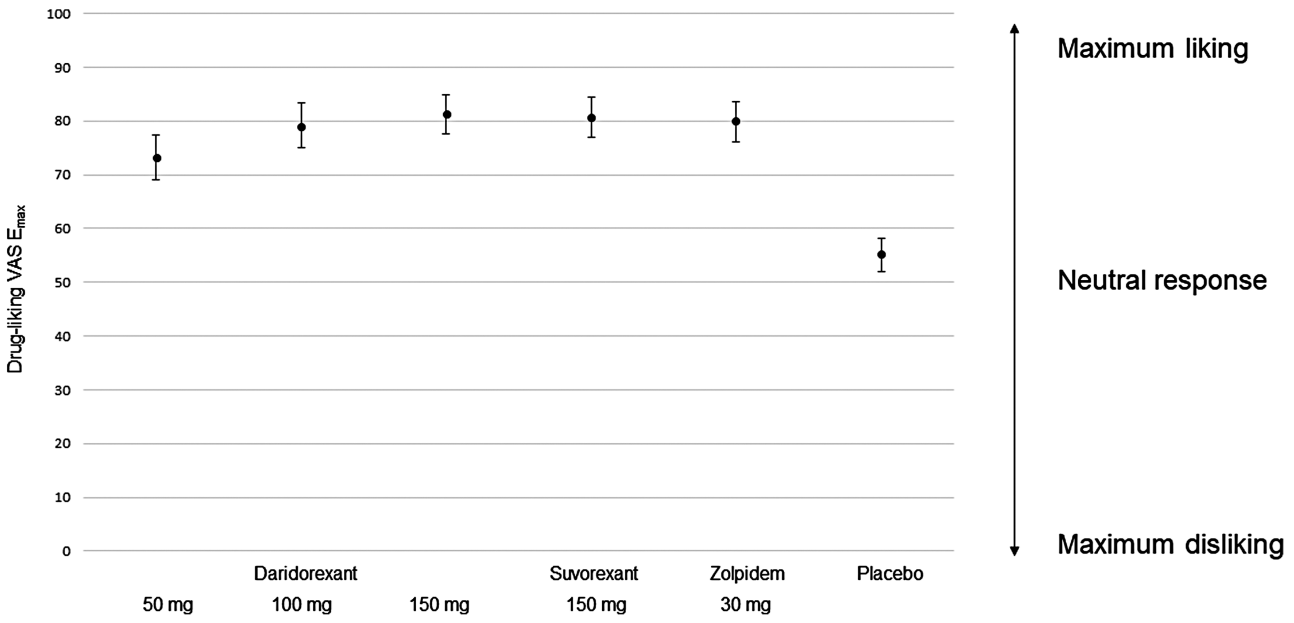


Figure 2. Drug-liking VAS E_{max} by treatment. Data are displayed as arithmetic mean and 95% CI.

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Table 2. Secondary PD endpoint data by treatment

		Daridorexant (mg)			Suvorexant (mg)	Zolpidem (mg)
	Comparison vs.	50	100	150	150	30
Subjective assessments of abuse-related effects						
Overall Drug-liking VAS (E_{max})	Placebo	18.6 (1.25)***	24.3 (1.63)***	27.5 (1.76)***	27.0 (1.86)***	25.0 (1.75)***
	Suvorexant	−5.5 (−0.60)*	−1.0 (−0.23)	1.0 (−0.07)	n.a.	n.a.
	Zolpidem	−4.0 (−0.44)*	0.0 (0.07)	1.0 (0.20)	n.a.	n.a.
Take Drug Again VAS (E_{max})	Placebo	19.4 (1.28)***	24.4 (1.50)***	25.9 (1.62)***	26.0 (1.70)***	25.0 (1.61)***
	Suvorexant	−3.5 (−0.47)*	−2.0 (−0.21)	1.0 (0.00)	n.a.	n.a.
	Zolpidem	−3.0 (−0.37)	2.0 (0.00)	2.0 (0.17)	n.a.	n.a.
Good Effects VAS (E_{max})	Placebo	37.3 (1.42)***	51.4 (1.92)***	57.7 (2.58)***	66.0 (2.25)***	60.5 (2.19)***
	Suvorexant	−18.2 (−0.79)***	−4.1 (−0.26)	2.2 (0.15)	n.a.	n.a.
	Zolpidem	−15.4 (−0.67)***	−1.4 (−0.06)	5.0 (0.24)	n.a.	n.a.
Feeling High VAS (E_{max})	Placebo	32.7 (1.26)***	42.9 (1.53)***	52.5 (2.10)***	59.0 (1.67)***	63.0 (2.26)***
	Suvorexant	−11.9 (−0.48)**	−1.7 (−0.10)	6.5 (0.40)	n.a.	n.a.
	Zolpidem	−21.9 (−0.90)***	−7.0 (−0.40)*	−2.1 (−0.08)	n.a.	n.a.
Any Effects VAS (E_{max})	Placebo	39.4 (1.48)***	54.2 (2.05)***	60.7 (2.78)***	75.5 (2.65)***	59.5 (2.34)***
	Suvorexant	−23.7 (−1.00)***	−8.8 (−0.52)**	−3.0 (−0.16)	n.a.	n.a.
	Zolpidem	−15.7 (−0.69)***	−0.8 (−0.04)	9.0 (0.25)	n.a.	n.a.
Bowdle VAS	Placebo	0.00 (0.41)*	0.20 (0.58)***	0.10 (0.73)***	0.1 (0.80)***	0.3 (1.18)***
Internal perception (E_{max})	Suvorexant	−0.10 (−0.22)**	0.00 (−0.04)*	0.00 (0.06)	n.a.	n.a.
	Zolpidem	−0.20 (−1.14)***	−0.20 (−0.83)***	−0.20 (−0.76)***	n.a.	n.a.
Bowdle VAS	Placebo	0.00 (0.44)*	0.10 (0.58)**	0.20 (0.76)***	0.2 (0.84)***	0.3 (1.29)***
External perception (E_{max})	Suvorexant	−0.10 (−0.37)***	0.00 (−0.18)*	0.00 (−0.17)	n.a.	n.a.
	Zolpidem	−0.20 (−1.13)***	−0.20 (−0.80)***	−0.20 (−0.85)***	n.a.	n.a.
Alertness/Drowsiness VAS (E_{min})	Placebo	−27.0 (−1.11)***	−37.0 (−1.89)***	−38.5 (−2.45)***	−34.5 (−2.13)***	−25.0 (−1.57)***
	Suvorexant	11.2 (0.90)***	1.7 (0.18)	−2.5 (−0.31)	n.a.	n.a.
	Zolpidem	4.6 (0.31)*	−2.0 (−0.39)	−9.4 (−0.81)	n.a.	n.a.
Investigator rated assessments of alertness/sedation						
OAA/S—composite score (E_{min})	Placebo	−0.70 (−1.24)***	−1.0 (−1.91)***	−1.0 (−1.91)***	−1.0 (−1.76)***	−1.3 (−2.50)***
	Suvorexant	0.50 (0.76)***	0.20 (0.29)	0.20 (0.27)	n.a.	n.a.
	Zolpidem	0.60 (1.08)***	0.30 (0.58)**	0.30 (0.55)**	n.a.	n.a.
OAA/S—sum score (E_{min})	Placebo	−2.0 (−1.08)***	−3.0 (−1.76)***	−3.1 (−2.08)***	−3.3 (−1.79)***	−3.9 (−2.46)***
	Suvorexant	1.6 (0.98)***	0.60 (0.43)*	0.10 (0.10)	n.a.	n.a.
	Zolpidem	2.2 (1.33)***	1.3 (0.87)***	1.0 (0.49)*	n.a.	n.a.
Objective assessments of cognitive function						
Five-choice reaction time (E_{max})	Placebo	16.5 (0.36)*	36.0 (0.78)***	29.5 (0.92)***	50.5 (1.00)***	111.0 (1.58)***
	Suvorexant	−43.3 (−0.69)***	−32.0 (−0.49)***	−14.8 (−0.33)	n.a.	n.a.
	Zolpidem	−94.5 (−0.92)***	−69.5 (−0.81)***	−63.0 (−0.71)***	n.a.	n.a.
RVP—response latency (E_{max})	Placebo	19.0 (0.44)**	27.0 (0.61)**	36.5 (0.75)***	57.0 (0.84)***	83.5 (1.19)***
	Suvorexant	−31.5 (−0.46)**	−14.5 (−0.15)	−8.5 (0.10)	n.a.	n.a.
	Zolpidem	−67.5 (−0.90)***	−35.0 (−0.57)***	−29.5 (−0.36)*	n.a.	n.a.
PAL—total errors (E_{max})	Placebo	1.0 (0.26)	4.0 (0.81)***	3.0 (1.01)***	5.4 (1.00)***	7.5 (1.50)***
	Suvorexant	−3.9 (−0.86)***	−0.9 (−0.24)	0.1 (0.01)	n.a.	n.a.
	Zolpidem	−6.0 (−1.26)***	−4.0 (−0.83)***	−3.0 (−0.75)**	n.a.	n.a.

This table displays differences of secondary PD endpoint data for comparisons between (1) each dose of the test drug daridorexant versus placebo, suvorexant, and zolpidem as well as (2) between suvorexant and zolpidem versus placebo. Five-choice reaction time and RVP—response latency are displayed in milliseconds. All other data are dimensionless. A one-sided alpha of 0.05 was applicable for comparisons between positive control drugs (i.e. suvorexant, zolpidem) and placebo or daridorexant. Significant differences are annotated (*$p < 0.05$; **$p < 0.005$; ***$p < 0.0005$). A two-sided alpha of 0.10 was applicable for comparisons between daridorexant and placebo. Significant differences are annotated (*$p < 0.1$; **$p < 0.01$; ***$p < 0.001$). The respective significance levels are also color-coded (*light gray; **gray; ***dark gray). Effect estimates (Cohen's *D*) are provided in parentheses and have been calculated as quotient of the mean treatment difference and estimates for within-subject standard deviation from a mixed-effects model [43]. n.a., not applicable; n.s., not significant.

Any Effects VAS scores of all active treatments were significantly higher than those of placebo and daridorexant again showed significantly lower scores than both control drugs at the dose of 50 mg, which also applied to the dose of 100 mg in comparison to suvorexant.

Sedative effects Sedative effects were evaluated based on the bipolar Alertness/Drowsiness VAS and the investigator rated OAA/S with lower scores indicating greater sedation. All active treatments clearly differentiated from placebo with a time to E_{min} of approximately 1–2 h post dosing. Regarding Alertness/Drowsiness VAS data, daridorexant exhibited dose-related sedative effects that were at the dose of 50 mg significantly lower than those of suvorexant or zolpidem, but not different from both control drugs at supratherapeutic doses of 100 and 150 mg. Sedative effects determined based on the investigator rated OAA/S were highest for zolpidem, but generally not very pronounced (data not shown).

Drug similarity effects The perceived effects of both control drugs and daridorexant were consistently considered most similar to

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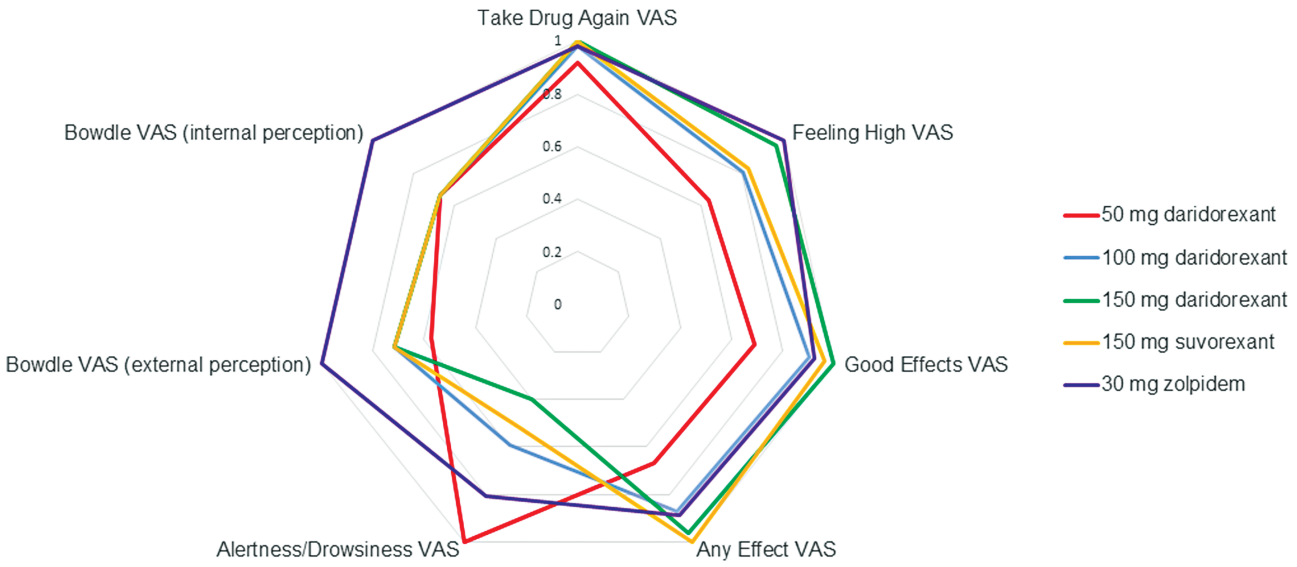


Figure 3. Radar chart of subjective secondary PD VAS data. This radar chart displays mean E_{min} (Alertness/Drowsiness VAS) and E_{max} (all other VAS) values by active treatment. For each endpoint, the treatment with the highest score has been used as reference (i.e. score of 1) and data for the other treatments have been calculated as quotient (i.e. treatment score divided by reference score). Note that lower scores of the Alertness/Drowsiness VAS represent greater sedative effects and vice versa. Treatment differences for the Bad Effects VAS are not reported given the low magnitude of responses on this measure (i.e. median E_{max} of 0.0 for all treatments).

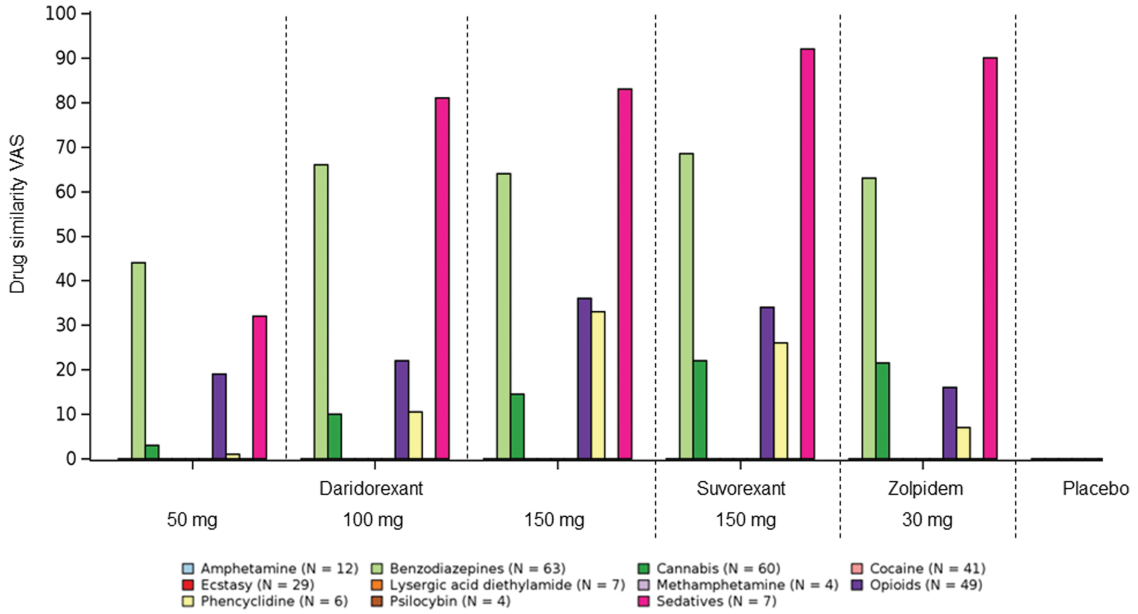


Figure 4. Drug similarity VAS by treatment. Data are displayed as median score obtained at 12 h post dosing and have been determined on a unipolar scale ranging from 0 (=not at all similar) to 100 points (= very similar). The number of participants with reported previous use of any of these drugs or classes of drugs for recreational purposes is provided in parentheses. Data are restricted to drugs or classes of drugs for which at least two participants had reported previous use. The category of "Sedatives" corresponds to non-benzodiazepine/non-barbiturate sedatives (e.g. zolpidem, zopiclone).

those of benzodiazepines and other non-benzodiazepine/non-barbiturate sedatives (e.g. zolpidem, zopiclone). VAS scores with respect to benzodiazepines and other sedatives were lowest at the 50 mg dose of daridorexant compared to all other active treatments (Figure 4).

Cognitive effects Both positive control drugs showed significant cognitive impairment with respect to most endpoints, including RTI—five-choice reaction time, RVP—response latency, and PAL—total errors. Compared to zolpidem, daridorexant showed significantly less impairment at all doses, while in comparison to suvorexant this was applicable only for the lowest dose of 50 mg daridorexant. There was no evidence of systematic time-dependent changes of cognitive effect data indicating absence of practice effects irrespective of treatment (data not shown).

PK results

Peak plasma concentrations of daridorexant were reached approximately 1 h postdose (i.e. t_{max}) and thereafter declined in an apparently biphasic manner with an elimination half-life (i.e. $t_{1/2}$) ranging from approximately 7 to 9 h. Peak (i.e. C_{max}) and overall

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exposure (i.e. $AUC_{0-24\,h}$ and $AUC_{0-\infty}$) increased dose dependently across the three doses administered (Table 3 and Figure 5).

PK/PD results

The potential relationship between the C_{max} of daridorexant and the Drug-liking VAS E_{max} was evaluated by linear regression analysis across all three tested doses, which indicated no correlation ($r^2 = 0.0035$, $p = 0.4167$).

Safety results

After administration of daridorexant, the overall AE incidence in the core phase dose dependently increased from 58.2% (50 mg) to 79.7% (100 mg) to 86.1% (150 mg), while it was 83.6% and 92.8% for suvorexant and zolpidem, respectively, and 24.2% for placebo (Table 4).

Somnolence was the most reported AE with a dose-related incidence of 44.8% (50 mg), 59.4% (100 mg), and 80.6% (150 mg) following administration of daridorexant as compared to 68.7% and 53.6% after administration of suvorexant and zolpidem, respectively (Table 4).

Notably, the most common euphoria-related AEs as defined by FDA guidance [26] with an overall incidence >10% (i.e. euphoric mood, feeling abnormal) were less frequent at all doses of daridorexant (3.0%–5.8%) as compared to suvorexant (9.0%) and zolpidem (20.3%) (Table 4).

Apart from euphoric mood, other psychiatric disorders were confusional state and visual hallucinations. These were markedly more frequent following administration of zolpidem as compared to suvorexant and daridorexant. Conversely, sleep paralysis was more frequent following administration of both DORAs compared to zolpidem (Table 4).

There was a single participant with serious AEs of suicidal behavior and substance-induced psychotic disorder that were not considered to be study drug related, as these occurred 1 week after last dosing (50 mg daridorexant) and following consumption of multiple illicit drugs after release from the study site. In the core phase of this study, only a single participant had to be discontinued due to an AE of paresthesia after administration of zolpidem. Here, ongoing AEs of photopsia and toothache after administration of 150 mg daridorexant in the preceding period also contributed to the participant's decision to discontinue.

There were no clinically relevant changes of vital sign, ECG, C-SSRS, and clinical laboratory data during the core phase of this study except for a single participant with increased alanine and aspartate aminotransferases at the end-of-study visit (i.e. 4 days after 100 mg daridorexant).

The safety profiles of suvorexant and zolpidem during the qualification phase were similar to those obtained during the core phase (data not shown).

Table 3. PK parameters of daridorexant by dose

Parameter (unit)	Daridorexant (50 mg)	Daridorexant (100 mg)	Daridorexant (150 mg)
C_{max} (ng/mL)	1115 (1012–1229)	1653 (1524–1794)	1958 (1812–2116)
t_{max} (h)	1.1 (0.55–6.1)	1.1 (0.55–4.1)	1.1 (0.33–4.1)
$AUC_{0-24\,h}$ (ng h/mL)	6715 (6067–7431)	11 597 (10 560–12 735)	15 421 (14 117–16 845)
$AUC_{0-\infty}$ (ng h/mL)	7692 (6804–8697)	13 848 (12 365–15 508)	18 983 (16 900–21 323)
$t_{1/2}$ (h)	7.5 (6.7–8.3)	8.7 (7.8–9.6)	9.3 (8.3–10.4)

Data are displayed as geometric means (95% CI) except for t_{max} which is provided as median (range).

Discussion

In this large, valid HAP study, daridorexant exhibited dose-related drug-liking effects that were lower compared to supratherapeutic doses of the control drugs zolpidem and suvorexant at the highest phase-3 dose of 50 mg. However, these effects were similar to both control drugs at supratherapeutic doses of daridorexant. Drug-liking effects of both control drugs and all doses of daridorexant were distinguishable from placebo.

As required per FDA guidance, a hierarchical hypothesis testing approach was applied in this HAP study by order of assessing (1) study validity (i.e. control drugs vs. placebo), (2) relative abuse potential (i.e. control drug vs. test drug), followed by (3) absolute abuse potential (i.e. test drug vs. placebo) [26]. Consequently, study validity is required to allow for subsequent assessment of relative and absolute abuse potential, and it is hence critical to a priori define the applicable validity margin and calculate the required sample size accordingly. In the present study, a minimum of 60 evaluable participants completing all six study periods in the core phase were required, which is considerably higher than the sample size in most HAP studies conducted prior finalization of the FDA guidance typically ranging from approximately 30 to 40 participants. Consequently, predefined study validity criteria were fully met in this study as evidenced by drug-liking effects of both control drugs clearly differentiating from placebo (i.e. lower bound of the 95% CI for the mean difference from placebo >15 points for both control drugs). The selected validity margin of 15 points has been applied as recommended by FDA in context of abuse-deterrent opioids [44]. It is hence a rather conservative margin and its appropriateness for schedule IV control drugs has been challenged in context of the lemborexant HAP study that failed on validity at the 15-point margin. Therefore, a post hoc analysis based on an 11-point margin was conducted and used to derive conclusions from that HAP study [28, 29].

Apart from the confirmation of validity, the robustness of the present HAP study is further indicated by a consistent pattern of primary and secondary PD results. Daridorexant exhibited dose-related responses both on primary and most secondary PD endpoints generally indicative of a lower abuse potential compared to both control drugs at the dose of 50 mg, but similar responses at 100 and 150 mg. Suvorexant, zolpidem, and all doses of daridorexant differentiated from placebo with respect to most secondary PD endpoints. In line with the drug classes and their mechanisms of action, sedative effects were noted, and the effects were perceived similar to those of benzodiazepines and other sedatives previously used for recreational purposes by the study participants.

In contrast to most HAP studies, two positive control drugs were used in the present study. Suvorexant was selected as it

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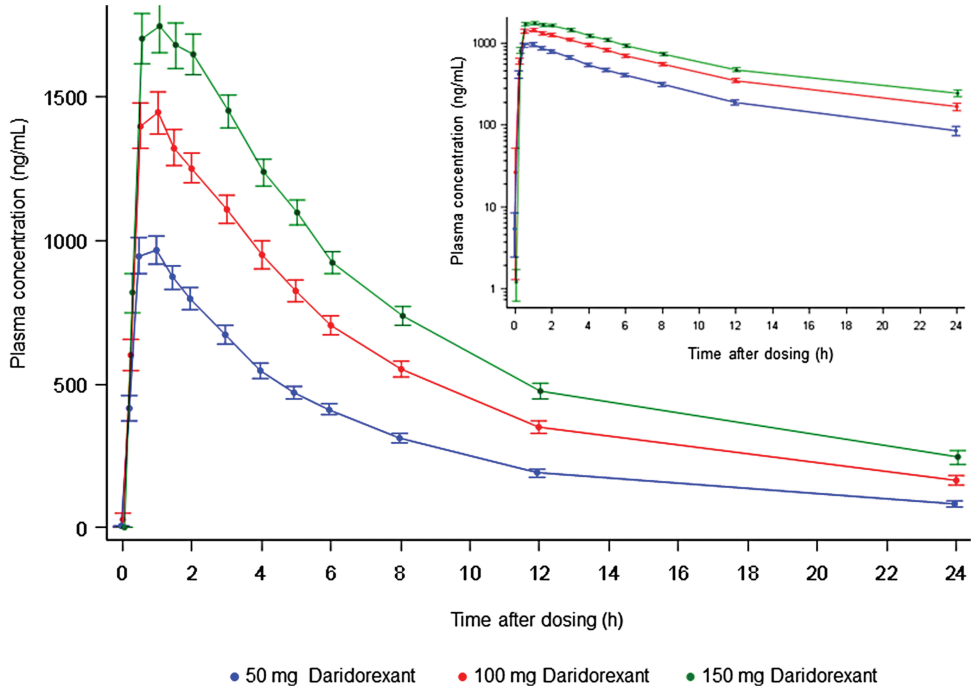


Figure 5. Plasma concentration–time profile of daridorexant by dose. Data are displayed as arithmetic mean concentrations by dose on a linear and semilogarithmic scale (inset) with error bars representing standard deviations.

Table 4. Incidence of AEs by treatment

System organ class MedDRA Preferred Term	Daridorexant (50 mg) (*n* = 67)	Daridorexant (100 mg) (*n* = 69)	Daridorexant (150 mg) (*n* = 67)	Suvorexant (150 mg) (*n* = 67)	Zolpidem (30 mg) (*n* = 69)	Placebo (*n* = 66)	Overall (*n* = 71)
Any AE	39 (58.2)	55 (79.7)	59 (86.1)	56 (83.6)	64 (92.8)	16 (24.2)	70 (98.6)
Nervous system disorders	33 (49.3)	46 (66.7)	56 (83.6)	49 (73.1)	47 (68.1)	11 (16.7)	69 (97.2)
Somnolence	30 (44.8)	41 (59.4)	54 (80.6)	46 (68.7)	37 (53.6)	3 (4.5)	68 (95.8)
Headache	7 (10.4)	6 (8.7)	5 (7.5)	5 (7.5)	6 (8.7)	7 (10.6)	25 (35.2)
Sleep paralysis	2 (3.0)	7 (10.1)	4 (6.0)	9 (13.4)	1 (1.4)	1 (1.5)	19 (26.8)
Dizziness	1 (1.5)	2 (2.9)	1 (1.5)	1 (1.5)	4 (5.8)	1 (1.5)	7 (9.9)
Psychiatric disorders	4 (6.0)	6 (8.7)	4 (6.0)	9 (13.4)	27 (39.1)	1 (1.5)	36 (50.7)
Euphoric mood	2 (3.0)	4 (5.8)	3 (4.5)	6 (9.0)	14 (20.3)	1 (1.5)	24 (33.8)
Confusional state	1 (1.5)	0	1 (1.5)	0	8 (11.6)	0	10 (14.1)
Hallucination, visual	0	0	0	1 (1.5)	4 (5.8)	0	5 (7.0)
General disorders/administration site conditions	4 (6.0)	6 (8.7)	10 (14.9)	9 (13.4)	20 (29.0)	0	31 (43.7)
Feeling abnormal	1 (1.5)	1 (1.4)	1 (1.5)	3 (4.5)	10 (14.5)	0	15 (21.1)
Fatigue	2 (3.0)	3 (4.3)	4 (6.0)	2 (3.0)	2 (2.9)	0	9 (12.7)
Eye disorders	3 (4.5)	2 (2.9)	5 (7.5)	6 (9.0)	22 (31.9)	0	28 (39.4)
Diplopia	1 (1.5)	0	3 (4.5)	4 (6.0)	18 (26.1)	0	23 (32.4)
Metamorphopsia	0	0	0	0	5 (7.2)	0	5 (7.0)
Gastrointestinal disorders	4 (6.0)	8 (11.6)	7 (10.4)	6 (9.0)	7 (10.1)	4 (6.1)	22 (31.0)
Nausea	1 (1.5)	2 (2.9)	1 (1.5)	2 (3.0)	6 (8.7)	0	10 (14.1)
Respiratory, thoracic, and mediastinal disorders	0	1 (1.4)	1 (1.5)	0	7 (10.1)	0	9 (12.7)
Hiccups	0	0	0	0	7 (10.1)	0	7 (9.9)

The incidence of AEs per MedDRA Preferred Term and system organ class is provided in descending order of frequency and restricted to AEs with a system organ class incidence >10%.

belongs to the same pharmacological class as daridorexant and is a schedule IV compound under the Controlled Substances Act. The schedule IV non-BZRA zolpidem was selected as benchmark control drug given its well-established drug-liking effects in multiple previous HAP studies thereby facilitating cross-study comparisons. Accordingly, each participant had to report drug-liking effects greater than placebo for both control drugs in order to qualify for this study (i.e. >65 points and >15 points higher than on placebo). This double qualification for two sedative control drugs with a different mechanism of action has led to a very stringent selection of participants indicated by a pass rate in the qualification phase of 32%, which is lower than the expected range of 45%–65% previously reported for HAP studies with a single control drug [45]. The general concept of

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qualifying participants based on their drug-liking of control drugs with similar properties as the test drug leads to a study population that may be at greatest risk of perceiving drug-liking effects of the test drug. In turn, this may hamper the translatability of the study data to the target patient population of patients with insomnia who may be less prone to perceive drug-liking or other abuse-related effects. Yet, these regulatory HAP studies are conceptually designed to minimize the risk of false negative results (i.e. to wrongly conclude on the lack of abuse potential that truly exists), even though it may be more relevant from a public health perspective to address the risk of abuse in the general population.

In terms of safety and tolerability, the overall AE profile of daridorexant and of both control drugs in the present HAP study was generally in line with their known pharmacology as sleep-promoting compounds (Table 4). For the abuse potential assessment, the incidence of AEs indicative of euphoria or other abuse-related effects appears particularly relevant. Here, euphoric mood and feeling abnormal were the only euphoria-related AEs per FDA guidance definition with an overall incidence >10%. These AEs were less frequent at all doses of daridorexant as compared to suvorexant and zolpidem (Table 4). In the first-in-human dose escalation study, daridorexant did not exhibit any euphoria-related AEs up to a single dose of 200 mg [33].

As the HAP studies with suvorexant and lemborexant were similar in terms of design compared to the present HAP study (e.g. crossover design, selection of primary endpoint, study population), it is intriguing to pursue cross-study comparisons of drug-liking data. Results from the suvorexant HAP study have previously been reported [27]. In case of the more recently approved DORA lemborexant, key study results are also publicly available, but have to be interpreted with caution since this study failed on validity and a full manuscript is still pending [28, 29].

In the suvorexant HAP study, single supratherapeutic doses of 40, 80, and 150 mg suvorexant exhibited drug-liking effects greater than placebo and similar to the positive control drug zolpidem (15 and 30 mg). Notably, these effects were not dose related with mean Drug-liking VAS E_{max} scores expressed as difference from placebo ranging from 22.8 (40 mg), 22.0 (80 mg), to 20.4 (150 mg). It remains uncertain whether the observed lack of dose–response represents a compound characteristic thereby suggesting relevant drug-liking already at therapeutic doses or whether it is rather due to the selected dose range being 2–7.5-fold in excess of the highest therapeutic dose, i.e. suggesting exploration of potentially saturated effects.

In the lemborexant HAP study, drug-liking effects of 10, 20, and 30 mg lemborexant were dose related, greater than placebo, and essentially similar to both control drugs, namely suvorexant (40 mg) and zolpidem (30 mg). At the top dose of 30 mg, Drug-liking VAS E_{max} scores were even significantly higher compared to suvorexant. Therefore, FDA Controlled Substance Staff concluded that the "*abuse potential of lemborexant may be similar to zolpidem but larger than suvorexant*" [29].

Contemplating drug-liking data from both HAP studies with suvorexant and lemborexant as well as from the present HAP study with daridorexant, this would overall be suggestive of lemborexant having the greatest abuse potential. However, comparisons across these HAP studies should be interpreted with caution due to intersubject variability and a different qualification procedure based on the response to zolpidem alone (suvorexant HAP study) versus response to zolpidem and suvorexant (lemborexant and daridorexant HAP studies).

HAP studies are often requested by FDA as part of the drug approval process for CNS active drugs. Though HAP study data are critical for any scheduling decision, it is only one piece in the overall assessment of abuse and dependence potential that is based on a comprehensive evaluation of all relevant preclinical and clinical data. This includes information about structural similarity to other drugs of abuse, preclinical data primarily from receptor profiling and animal behavioral studies, and other relevant clinical data, e.g. regarding the incidence of abuse-related AEs and withdrawal effects following cessation of drug intake after long-term exposure. The totality of these data is then summarized in the so-called eight-factor analysis of abuse potential prepared by the Controlled Substances Staff within FDA and forms the basis for deciding about the need for scheduling in the United States according to the Controlled Substances Act [46, 47].

In terms of preclinical data relevant for scheduling, daridorexant did not exhibit any abuse or dependence potential in the three key behavioral animal studies (i.e. self-administration, drug discrimination, dependence potential) [48]. This is in line with corresponding data for suvorexant that did not exhibit positive reinforcing effects in monkeys, cross-generalization to zolpidem or morphine, nor withdrawal symptoms indicating dependence potential in rats [49]. Lack of abuse and dependence potential in such animal behavioral studies has also been determined in case of lemborexant [29].

These preclinical data also comply with the biology of orexin peptides. Here, the functional role of orexin receptors has been reported to differ between subtypes with the orexin-2 receptor being more strongly associated with the modulation of wakefulness and sleep than the orexin-1 receptor which has been shown to be involved in reward processing [10]. Accordingly, blockade of orexin-1 receptors with selective antagonists as well as by the DORA suvorexant, resulted in reduced self-administration in rodents [18, 19]. Therefore, DORAs are even under investigation as potential treatment of cocaine related or other substance use disorders [50].

In the recently completed phase-3 trials with daridorexant including 1854 patients with insomnia disorder, the incidence of predefined abuse-associated events was balanced across all doses of daridorexant and placebo. In addition, there were no withdrawal effects based on the Benzodiazepine Withdrawal Symptoms Questionnaire indicating lack of dependence potential [48]. Overall, this suggests a very low potential for abuse of daridorexant which complies with postmarketing data of suvorexant extracted from the FDA Adverse Events Reporting System (FAERS). Here, only 32 cases of intentional product misuse were identified for suvorexant from its approval in 2014 until June 30, 2020, suggesting lack of relevant abuse under real-life conditions [51]. Regardless, suvorexant has been assigned to schedule IV which was largely based on HAP study results prior market launch of this first-in-class compound, i.e. in absence of any postmarketing data [52]. Notably, there are other CNS depressant compounds that have also shown drug-liking effects greater than placebo and similar to control drugs in the respective HAP studies that yet belong to schedule V such as the antiepileptics pregabalin [53, 54] or lacosamide [55–57].

In conclusion, daridorexant showed dose-related drug-liking in this large, valid HAP study with lower effects at the

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highest phase-3 dose of 50 mg compared to supratherapeutic doses of suvorexant and zolpidem, but similar effects at doses of 100 and 150 mg daridorexant. The translatability and relevance of these data from recreational sedative drug users for the target population of patients with insomnia may be limited given the lack of any abuse signal in the recently completed phase-3 program. In the end, the totality of relevant preclinical and clinical data obtained with daridorexant as well as real-world evidence from other DORAs should be considered for a well-informed assessment of its abuse and dependence potential and for an appropriate scheduling decision.

Supplementary Material

Supplementary material is available at *SLEEP* online.

Supplementary Figure 1. Study design. The study design is schematically displayed for the three-period qualification phase and the six-period core phase. Each study period was separated by a ≥72 h washout. Participants remained domiciled for the entire duration of the qualification and core phase, i.e. until at least 24 h after last dosing and returned for an end-of-study visit ≥72 h after last dosing.

Supplementary Table 1. Schedule of PD assessments—qualification and core phase. The postdose time points are displayed for each PD assessment. These were identical for qualification and core phase.

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Authors' Contributions

MU wrote the manuscript which has been reviewed by all authors. MU, KS, and JD designed the research. MU and KS analyzed the data. DK performed the research.

Disclosure Statement

None declared.

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