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Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

*Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators**

Summary

Background Daytime functioning is impaired in people with insomnia disorder. Currently available dual orexin receptor antagonists have shown efficacy in insomnia disorder, but do not address all aspects of this disease. We aimed to assess safety and efficacy of daridorexant, a novel orexin receptor antagonist, on night-time and daytime symptoms of insomnia.

Methods We did two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials at 156 sites in 17 countries. Adults (aged ≥18 years) with insomnia disorder were randomly assigned using interactive response technology (1:1:1) to receive daridorexant 50 mg, 25 mg, or placebo (study 1) or daridorexant 25 mg, 10 mg, or placebo (study 2) every evening for 3 months. Participants, investigators, and site personnel were masked to treatment allocation. The primary endpoints were change from baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS), measured by polysomnography, at months 1 and 3. The secondary endpoints were change from baseline in self-reported total sleep time and the sleepiness domain score of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) at months 1 and 3. Study-wise type I error rate (5%) was controlled for all pairwise comparisons. Efficacy was analysed in all randomly assigned participants, and safety in all participants who received at least one dose of treatment. The studies are registered at ClinicalTrials.gov, NCT03545191 (study 1) and NCT03575104 (study 2).

Findings Between June 4, 2018 and Feb 25, 2020, 930 participants were randomly assigned to receive daridorexant 50 mg (n=310), daridorexant 25 mg (n=310), or placebo (n=310) in study 1. Between May 29, 2018, and May 14, 2020, 924 participants were randomly assigned to receive daridorexant 25 mg (n=309), daridorexant 10 mg (n=307), or placebo (n=308) in study 2. In study 1, WASO and LPS were significantly reduced among participants in the daridorexant 50 mg group compared with participants in the placebo group at month 1 (least squares mean [LSM] difference –22·8 min [95% CI –28·0 to –17·6], p<0·0001 for WASO; –11·4 min [–16·0 to –6·7], p<0·0001 for LPS) and month 3 (–18·3 min [–23·9 to –12·7], p<0·0001 for WASO; –11·7 min [–16·3 to –7·0], p<0·0001 for LPS). WASO and LPS were significantly reduced among participants in the daridorexant 25 mg group compared with the placebo group at month 1 (LSM difference –12·2 min [–17·4 to –7·0], p<0·0001 for WASO; –8·3 min [–13·0 to –3·6], p=0·0005 for LPS) and month 3 (–11·9 min [–17·5 to –6·2], p<0·0001 for WASO; –7·6 min [–12·3 to –2·9], p=0·0015 for LPS). Compared with placebo, participants in the daridorexant 50 mg group had significantly improved self-reported total sleep time at month 1 (LSM difference 22·1 min [14·4 to 29·7], p<0·0001) and month 3 (19·8 min [10·6 to 28·9], p<0·0001), and IDSIQ sleepiness domain scores at month 1 (–1·8 [–2·5 to –1·0], p<0·0001) and month 3 (–1·9 [–2·9 to –0·9], p=0·0002). Compared with the placebo group, participants in the daridorexant 25 mg group had significantly improved self-reported total sleep time at month 1 (LSM difference 12·6 min [5·0 to 20·3], p=0·0013) and month 3 (9·9 min [0·8 to 19·1], p=0·033), but not IDSIQ sleepiness domain scores (–0·8 [–1·5 to 0·01], p=0·055 at month 1; –1·0 [–2·0 to 0·01], p=0·053 at month 3). In study 2, WASO was significantly reduced among participants in the daridorexant 25 mg group compared with participants in the placebo group at month 1 (LSM difference –11·6 min [–17·6 to –5·6], p=0·0001) and month 3 (–10·3 min [–17·0 to –3·5], p=0·0028), whereas no significant differences in LPS were observed at month 1 (–6·5 min [–12·3 to –0·6], p=0·030) or month 3 (–9·0 [–15·3 to –2·7], p=0·0053). Compared with the placebo group, participants in the daridorexant 25 mg group had significant improvement in self-reported total sleep time at month 1 (LSM difference 16·1 min [8·2 to 24·0], p<0·0001) and month 3 (19·1 [10·1 to 28·0], p<0·0001), but not in IDSIQ sleepiness domain scores (–0·8 [–1·6 to 0·1], p=0·073 at month 1; –1·3 [–2·2 to –0·3], p=0·012 at month 3). Compared with the placebo group, no significant differences were observed among participants in the daridorexant 10 mg group for WASO (LSM difference –2·7 min [–8·7 to 3·2], p=0·37 at month 1; –2·0 [–8·7 to 4·8], p=0·57 at month 3), LPS (–2·6 min [–8·4 to 3·2], p=0·38 at month 1; –3·2 min [–9·5 to 3·1], p=0·32 at month 3), self-reported total sleep time (13·4 min [5·5 to 21·2], p=0·0009 at month 1; 13·6 min [4·7 to 22·5], p=0·0028 at month 3), nor IDSIQ sleepiness domain scores (–0·4 [–1·3 to 0·4], p=0·30 at month 1; –0·7 [–1·7 to 0·2], p=0·14 at month 3). Overall incidence of adverse events was comparable between treatment groups (116 [38%] of 308 participants in the daridorexant 50 mg group, 117 [38%] of 310 in the daridorexant 25 mg group, and 105 [34%]

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This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on January 20, 2022

See **Comment** page 104

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See **Online** for appendix

of 309 in the placebo group in study 1; 121 [39%] of 308 participants in the daridorexant 25 mg group, 117 [38%] of 306 in the daridorexant 10 mg group, and 100 [33%] of 306 in the placebo group). Nasopharyngitis and headache were the most common adverse events in all groups. One death (cardiac arrest) occurred in the daridorexant 25 mg group in study 1, which was not deemed to be treatment-related.

Interpretation Daridorexant 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favourable safety profile.

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Introduction

Insomnia disorder is characterised by difficulties in initiating or maintaining sleep, and is associated with distress or impairment in daytime functioning.[1,2] A wide range of daytime complaints, from fatigue and reduced energy to mood alteration and cognitive difficulties, are reported by people with insomnia.[2] Current treatment guidelines recommend cognitive behavioural therapy for insomnia as first-line treatment.[3–5] However, this treatment is not always accessible or desired by individuals with insomnia, and not all people derive benefit from it. Thus, sleep medications are often warranted. Among approved treatments for insomnia, GABA receptor agonists (including benzodiazepines [eg, eg, estazolam, flurazepam] and Z-drugs [eg, eszopiclone, zolpidem]) cause a global depression of the brain, often do not adequately address induction and maintenance of sleep, and have been associated with a risk of decreased efficacy with time

Research in context

Evidence before this study

We searched PubMed from database inception to May 31, 2021 for clinical trials, using the search terms "dual orexin receptor antagonist", "ACT-541468", "almorexant", "suvorexant", "lemborexant", and "filorexant", without language restrictions. Several randomised placebo-controlled trials have shown efficacy of dual orexin receptor antagonists on sleep endpoints in adult and older adult (aged ≥65 years) populations with primary insomnia or insomnia disorder, and these drugs have been generally well tolerated. However, to date, no dual orexin receptor antagonist has been developed without residual next-morning sedative effects. Daridorexant, selected for its optimum pharmacokinetic and pharmacodynamic properties, was developed as a novel dual orexin receptor antagonist to improve both sleep onset and sleep maintenance while being eliminated quickly enough to avoid residual sedative effects in the morning. The results of two phase 2 dose-finding studies (NCT02839200 and NCT02841709) in adults and older adults with insomnia suggested daridorexant had effects on sleep induction and maintenance without residual effects the next morning. The hypothesis was that with this pharmacokinetic and pharmacodynamic profile, daridorexant might improve daytime functioning in insomnia. Previous trials reporting on daytime functioning used patient-reported outcome instruments, which have not been fully validated, and did not rigorously control the type I error rate.

Added value of this study

The two trials presented here assessed the effect of daridorexant for insomnia on sleep outcomes and daytime functioning. Daytime functioning was measured using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), which is a novel instrument validated according to US Food and Drug Administration guidelines. Additionally, in these two trials, the measure of daytime functioning was included as a secondary endpoint with rigorous control of the type I error rate. This secondary endpoint was based on a participant's daily self-assessment of how energetic, mentally and physically tired, or how sleepy they felt, but it was not an objective measure of sleepiness (such as the multiple sleep latency test). Using this new patient-reported outcome instrument, participants in the studies could report daily how they felt with regard to the three IDSIQ domains of sleepiness, mood, alert/cognition.

Implications of all the available evidence

Insomnia disorder not only affects night-time sleep, but also markedly alters daytime functioning and wellbeing. When treating people with insomnia, therefore, clinicians should pay attention to both the deficit in sleep and any reported alteration of daytime functioning. Moreover, new treatments for insomnia should be directed at improving both night-time and daytime symptoms. A prerequisite to achieve this goal is that a drug has no next-morning residual effect leading to excessive daytime somnolence, yet it adequately induces and maintains sleep. Daridorexant 50 mg seems to fulfil those requirements. Improvements in sleep variables were achieved without excess sleepiness the following morning, and improvements in daytime functioning were observed. The improvement in sleep perceived by participants in these studies was consistent with that objectively measured by polysomnography. Future studies should determine whether daridorexant can help reduce the negative consequences of loss of sleep, such as hypertension or Alzheimer's disease, and the negative consequences of altered daytime functioning, such as the risks of falls, depression, and memory loss.

(ie, tolerance) and dependence. Dual orexin receptor antagonists target the excessive wakefulness characteristic of insomnia and improve sleep variables, without some of the side-effects of GABA receptor agonists.[6,7] However, to our knowledge, no sleep medications have improved daytime functioning impairment, which is reported by people with insomnia. Furthermore, some treatments have been shown to increase daytime somnolence and impair daytime functioning, particularly in older people (aged ≥65 years).[8]

The novel dual orexin receptor antagonist, daridorexant, was designed as a medication for insomnia that would have efficacy for sleep onset and sleep maintenance but without any residual effects in the morning that might impair daytime functioning.[9] In phase 2 dose-finding trials, daridorexant improved sleep variables in adults and older adults (aged 65–85 years) with insomnia without causing residual sleepiness the next morning.[10,11] Therefore, we hypothesised that daridorexant might also improve daytime functioning.

Here, we present the results of two placebo-controlled phase 3 trials (study 1 and study 2), in which we aimed to assess the safety and efficacy of daridorexant in people with insomnia.

Methods

Study design

We did two multicentre, randomised, double-blind, placebo-controlled, parallel-group trials to assess the safety and efficacy of daridorexant in people with insomnia. Study 1 was performed at 75 hospitals and sleep centres in ten countries (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, and the USA). Study 2 was performed at 81 hospitals and sleep centres (different from study 1) in 11 countries (Belgium, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hungary, South Korea, Sweden, and the USA). The trials consisted of a screening period (7–18 days), a single-blind placebo run-in period (13–24 days), a double-blind treatment period (3 months), and a single-blind placebo run-out period (7 days), followed by either a safety follow-up period (23 days) or participation in a 9-month placebo-controlled extension trial (NCT03679884; results of which will be reported elsewhere; appendix p 24).

Both trials were done in accordance with the trial protocols (appendix pp 51, 205), the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and local regulations. The study protocols were developed by the study sponsor with guidance from an expert advisory group (appendix p 6) and were approved by an institutional review board or ethics committee.

Participants

Participants were enrolled by site investigators. Eligible participants were adults (aged ≥18 years) who had insomnia disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition [DSM-5][1]) that was of moderate or severe intensity at screening (Insomnia Severity Index score ≥15). An additional inclusion criterion was a self-reported history of disturbed sleep (ie, all the following: ≥30 min to fall asleep, ≥30 min awake during sleep time, and self-reported total sleep time of ≤6·5 h) on at least three nights per week for at least 3 months before screening. During the placebo run-in period, these self-reported sleep parameters were also required to be met on at least three of seven nights. Moreover, during the placebo run-in period, polysomnography criteria had to be met (ie, all the following: latency to persistent sleep [LPS] ≥20 min, wake time after sleep onset [WASO] ≥30 min, and mean total sleep time of <7 h).

Participants were excluded if they met any of the following criteria: self-reported daytime napping (≥1 h per day on ≥3 days per week); a history of suicidal ideation or attempt, acute or chronic psychiatric condition not controlled by therapy, severe depression, or alcohol or drug misuse; an apnoea or hypopnoea index of 15 events per h or higher (per American Academy of Sleep Medicine criteria) or an event associated with oxygen saturation of less than 80% (assessed by polysomnography); or periodic limb movement index of 15 or more events per h (assessed by polysomnography), restless legs syndrome, circadian rhythm disorder, rapid-eye-movement behaviour disorder, or narcolepsy. A full list of inclusion and exclusion criteria is provided in the appendix (p 9). All participants provided written informed consent.

For **American Academy of Sleep Medicine criteria** see http://www.aasmnet.org

Randomisation and masking

In study 1, participants were randomly assigned (1:1:1) to receive daridorexant 25 mg, daridorexant 50 mg, or placebo. In study 2, participants were randomly assigned (1:1:1) to receive daridorexant 10 mg, daridorexant 25 mg, or placebo. Randomisation was stratified by age (<65 years and ≥65 years), and treatment was allocated using an interactive response technology system. A randomisation list was generated for each study by Almac Clinical Technologies (Souderton, PA, USA) and remained confidential until after database lock. Participants, investigators, site personnel, and sponsor-authorised personnel were unaware of treatment allocation. Only participants were masked to treatment during placebo run-in and run-out periods. Investigational treatment and matching placebo were indistinguishable, and all treatment wallets were packaged in the same way. In the event of a medical emergency, investigators were permitted to initiate the unmasking process; no unmasking events occurred in either study.

Procedures

In the placebo run-in period, polysomnography assessments were done on two consecutive nights on eligible participants who completed seven or more eDiary entries, defining baseline values. During the double-blind

treatment period, participants in study 1 received oral daridorexant 25 mg, daridorexant 50 mg, or placebo every evening for 3 months, and participants in study 2 received oral daridorexant 10 mg, daridorexant 25 mg, or placebo for 3 months. During the double-blind treatment period, participants attended two consecutive nights of polysomnography recording, at the end of months 1 and 3. A single-night polysomnography recording was performed during the first night of the placebo run-out period. Participants were required to complete daily eDiary entries throughout the trials, from screening to the end of the placebo run-out period. The eDiary (appendix p 16) included a morning and an evening questionnaire, morning and evening visual analogue scales, and the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), which was completed in the evening.

Development and validation of the IDSIQ has been described previously.[12] The domains and corresponding items of the IDSIQ are summarised in the appendix (p 25). The IDSIQ comprises 14 items with a recall period of today and was developed for completion every evening using an electronic hand-held device. Each item is scored on an 11-point numerical scale (from 0 to 10), with lower scores denoting better daytime functioning. As part of the quantitative validation of IDSIQ, the clinically important within-person change (also termed the responder definition) was determined to evaluate the clinical meaningfulness of the effect.[12] However, the clinically meaningful between-groups difference remains to be established. The items in IDSIQ are grouped into three domains reflecting daytime impairment of insomnia that are commonly encountered in clinical practice:[13,14] sleepiness domain (scores 0–40; whereby a ≥4-point reduction from baseline was considered to indicate a clinically meaningful within-person improvement), mood domain (scores 0–40; whereby a ≥4-point reduction from baseline was considered to indicate a clinically meaningful within-person improvement), and alert/cognition domain (scores 0–60; whereby a ≥9-point reduction from baseline was considered to indicate a clinically meaningful within-person improvement), with total score ranging from 0 to 140 (whereby a ≥20-point reduction from baseline was considered to indicate a clinically meaningful within-person improvement).

Safety data (including adverse events and serious adverse events) were collected throughout the trial from screening up to 30 days after the end of treatment, or until the date of enrolment into the extension trial. An independent safety board adjudicated blinded adverse events associated with narcolepsy-like symptoms or suicide or self-injury (appendix p 8). The full schedule of assessments is summarised in the appendix (p 12).

Outcomes

The primary endpoints were change from baseline in WASO and LPS at months 1 and 3, measured by polysomnography in a sleep laboratory (centrally assessed by an independent scorer; appendix p 15). The secondary endpoints were change from baseline in self-reported total sleep time and in the IDSIQ sleepiness domain score, using the eDiary, at months 1 and 3.

Other prespecified efficacy endpoints were change from baseline in other IDSIQ domain scores and total IDSIQ score at months 1 and 3, change from baseline in subjective WASO and latency to sleep onset (LSO) at months 1 and 3, and change from baseline in total sleep time at months 1 and 3, as measured by polysomnography. Other protocol-defined endpoints will be reported separately.

Prespecified exploratory endpoints included evening visual analogue scales for ability to function and daytime alertness, and morning visual analogue scales for depth and quality of sleep (mean of daily entries in the 7 days before polysomnography nights; appendix p 16). The proportion of sleep spent in each sleep phase (measured by polysomnography), and Insomnia Severity Index score, were also evaluated as exploratory endpoints. A complete list of predefined exploratory endpoints are reported in the protocol. Other protocol-defined exploratory endpoints not presented here will be reported separately.

Safety endpoints included adverse events reported by the investigators, independent safety board-adjudicated adverse events, next-morning residual effects (change from baseline in visual analogue scales-assessed morning sleepiness), and (on treatment cessation) rebound insomnia (change in WASO and LPS from baseline to first night of placebo run-out period, and change in self-reported total sleep time from baseline to the mean over 1 week of run-out) and withdrawal symptoms (assessed by the Benzodiazepine Withdrawal Symptom Questionnaire [BWSQ] from last assessment on double-blind treatment to the end of placebo run-out period, and occurrence of relevant adverse events). Suicidal intent based on the Columbia Suicide Severity Rating Scale was defined in the protocol as a safety endpoint.

Statistical analysis

Full details of the sample size calculation for each study are provided in the appendix (pp 147–149, 302–304). Briefly, based on a two-sample Z test and data from the two phase 2 dose-finding studies,[10,11] we estimated that at least 900 participants per study (study 1 and study 2) would be needed to provide 98·9% power to detect an effect size of 0·37 for a single hypothesis test. This calculation accounted for the Bonferroni correction for which alpha is halved and set to 2·5% (two-sided). However, as the number of null hypotheses (endpoints) to test increases (appendix pp 17, 18), the power decreases. Consequently, we calculated that 900 participants per study would provide at least 90% power to detect an effect size of 0·37 for testing nine independent null hypotheses per study.

The primary and secondary endpoints were analysed in the intention-to-treat population, defined as all participants who were randomly assigned. For the primary endpoints, WASO and LPS polysomnography values were the mean of recordings of two consecutive nights at each timepoint. For the secondary endpoints, self-reported total sleep time and IDSIQ sleepiness domain scores were the mean of the seven entries in the week before polysomnography recording nights. All available data were included in efficacy analyses according to the International Conference on Harmonisation Guideline for Good Clinical Practice. We used a linear mixed-effects model for repeated measures (MMRM) for analysis of each primary and secondary endpoint, and missing data for a participant were assumed to be similar to those for people in the same treatment group. The model was adjusted for the baseline value of each primary or secondary endpoint and included factors for age stratification (<65 years; ≥65 years), treatment (higher dose; lower dose; placebo), visit (month 1; month 3), interactions of treatment by visit, and baseline by visit. Results are reported as point estimates and non-multiplicity adjusted 95% CIs. The study-wise type I error rate was controlled at a two-sided 5% significance level using a Bonferroni-based gatekeeping procedure to adjust for multiplicity (appendix p 17).[15] First, the two distinct endpoint categories (ie, sleep maintenance [WASO] and sleep onset [LPS]) at month 1 were simultaneously tested, each at half of the two-sided 5% significance level. Second, the remaining hypotheses were tested following the predefined gatekeeping strategy summarised in the appendix (p 17). Although the amount of missing data was low (≤9·4% across all endpoints, timepoints, and treatment groups), we did sensitivity analyses on the primary and secondary endpoints to account for departures from the missing-at-random assumption of the MMRM (appendix p 21). We did a post-hoc analysis on log-transformed LPS values due to the approximately log-normal distribution of these data. The additional IDSIQ endpoints (mood domain, alert/cognition domain, and total scores), were analysed using the same methodology as the primary and secondary endpoints (ie, analysed in the ITT population), but comparisons between daridorexant and placebo were not adjusted for multiplicity. To facilitate clinical interpretation of the IDSIQ sleepiness domain, empirical distribution function curves for each treatment group at each timepoint were produced, as per the original statistical analysis plan. Safety endpoints were analysed in all participants who had received at least one dose of treatment.

All statistical analyses were done using SAS software (version 9.4). An independent data-monitoring committee was established to monitor safety and efficacy (appendix p 7). The studies are registered with ClinicalTrials.gov, NCT03545191 (study 1) and NCT03575104 (study 2).

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report.

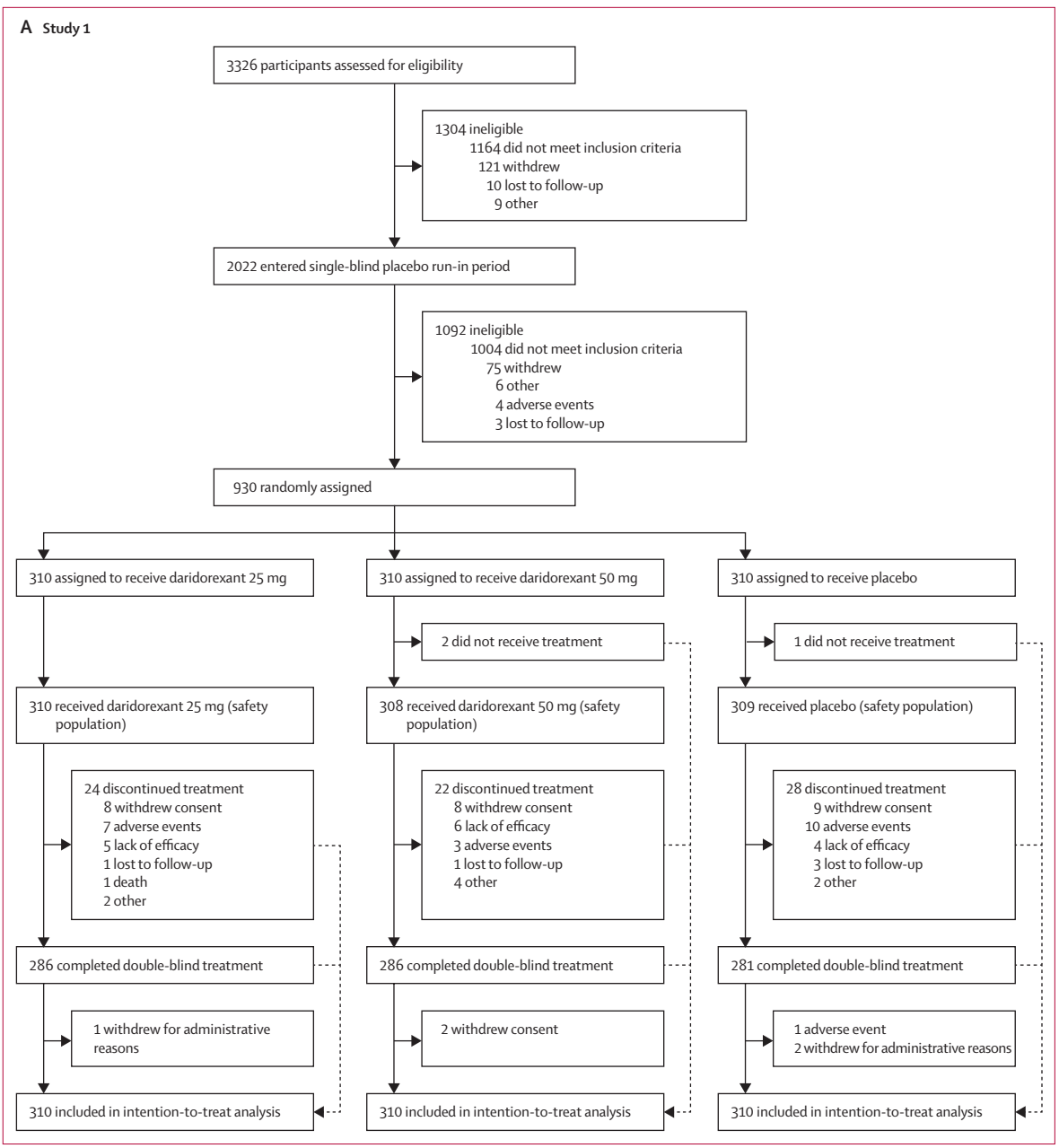
Results

Between June 4, 2018, and Feb 25, 2020, 3326 participants were screened for inclusion in study 1, of whom 930 were randomly assigned to receive daridorexant 25 mg (n=310), daridorexant 50 mg (n=310), or placebo (n=310). Between May 29, 2018, and May 14, 2020, 3683 participants were screened for inclusion in study 2, of whom 924 were randomly assigned to receive daridorexant 10 mg (n=307), daridorexant 25 mg (n=309), or placebo (n=308). The most common reasons for screening failure were either a high apnoea or hypopnoea index (≥15 events per h) or an event associated with blood oxygen saturation of less than 80%, or that the participant did not meet subjective sleep criteria (assessed by the eDiary) or objective sleep variable criteria (assessed by polysomnography during the run-in). Of the 930 participants randomly assigned in study 1, 853 (92%) completed double-blind treatment and of the 924 participants randomly assigned in study 2, 856 (93%) completed double-blind treatment (figure 1).

Demographics and baseline characteristics were balanced between treatment groups across both trials (table 1). Most participants were female (624 [67%] of 930 participants in study 1; 638 [69%] of 924 participants in study 2). 364 (39%) of 930 participants in study 1 and 363 (39%) of 924 participants in study 2 were aged 65 years or older. Of the 1854 participants included in studies 1 and 2, 1650 (89%) were White and 148 (8%) were Black or African American.

All randomly assigned participants were included in the intention-to-treat population (figure 1). The hypothesis testing results for the primary and secondary endpoints in each trial, including the thresholds for statistical significance, are summarised in the appendix (p 19).

In study 1, WASO was significantly reduced from baseline among participants in the daridorexant 50 mg group compared with participants in the placebo group at month 1 (least squares mean [LSM] difference –22·8 min [95% CI –28·0 to –17·6], p<0·0001) and month 3 (–18·3 min [–23·9 to –12·7], p<0·0001) and LPS was also significantly reduced from baseline compared with the placebo group at month 1 (LSM difference –11·4 min [95% CI –16·0 to –6·7], p<0·0001) and month 3 (–11·7 min [–16·3 to –7·0], p<0·0001; table 2, figure 2). Compared with placebo, self-reported total sleep time was significantly increased from baseline in the daridorexant 50 mg group at month 1 (LSM difference 22·1 min [95% CI 14·4 to 29·7], p<0·0001) and month 3 (19·8 min [10·6 to 28·9], p<0·0001) and IDSIQ sleepiness domain score was significantly reduced from baseline at month 1 (LSM difference –1·8 [95% CI –2·5 to –1·0], p<0·0001) and month 3 (–1·9 [–2·9 to –0·9]; p=0·0002; table 2, figure 3). In study 1,



(Figure 1 continues on next page)

WASO was significantly reduced among participants in the daridorexant 25 mg group compared with the placebo group at month 1 (LSM difference–12·2 min [95% CI –17·4 to –7·0], p<0·0001) and month 3 (–11·9 min [–17·5 to –6·2], p<0·0001) and LPS was also significantly reduced compared with the placebo group at month 1 (–8·3 min [–13·0 to –3·6], p=0·0005) and month 3 (–7·6 min [–12·3 to –2·9], p=0·0015). Compared with the placebo group, self-reported total sleep time was significantly increased in the daridorexant 25 mg group at month 1 (LSM difference 12·6 min [95% CI 5·0 to 20·3], p=0·0013) and month 3 (9·9 min [0·8 to 19·1], p=0·033); no significant difference in IDSIQ sleepiness domain score was identified between the groups at month 1 (LSM difference –0·8 [95% CI –1·5 to 0·01], p=0·055) or month 3 (–1·0 [–2·0 to 0·01], p=0·053; table 2, figures 2 and 3).

In study 2, WASO was significantly reduced among participants in the daridorexant 25 mg group compared with participants in the placebo group at month 1 (LSM difference –11·6 min [95% CI –17·6 to –5·6], p=0·0001) and month 3 (–10·3 min [–17·0 to –3·5], p=0·0028) and

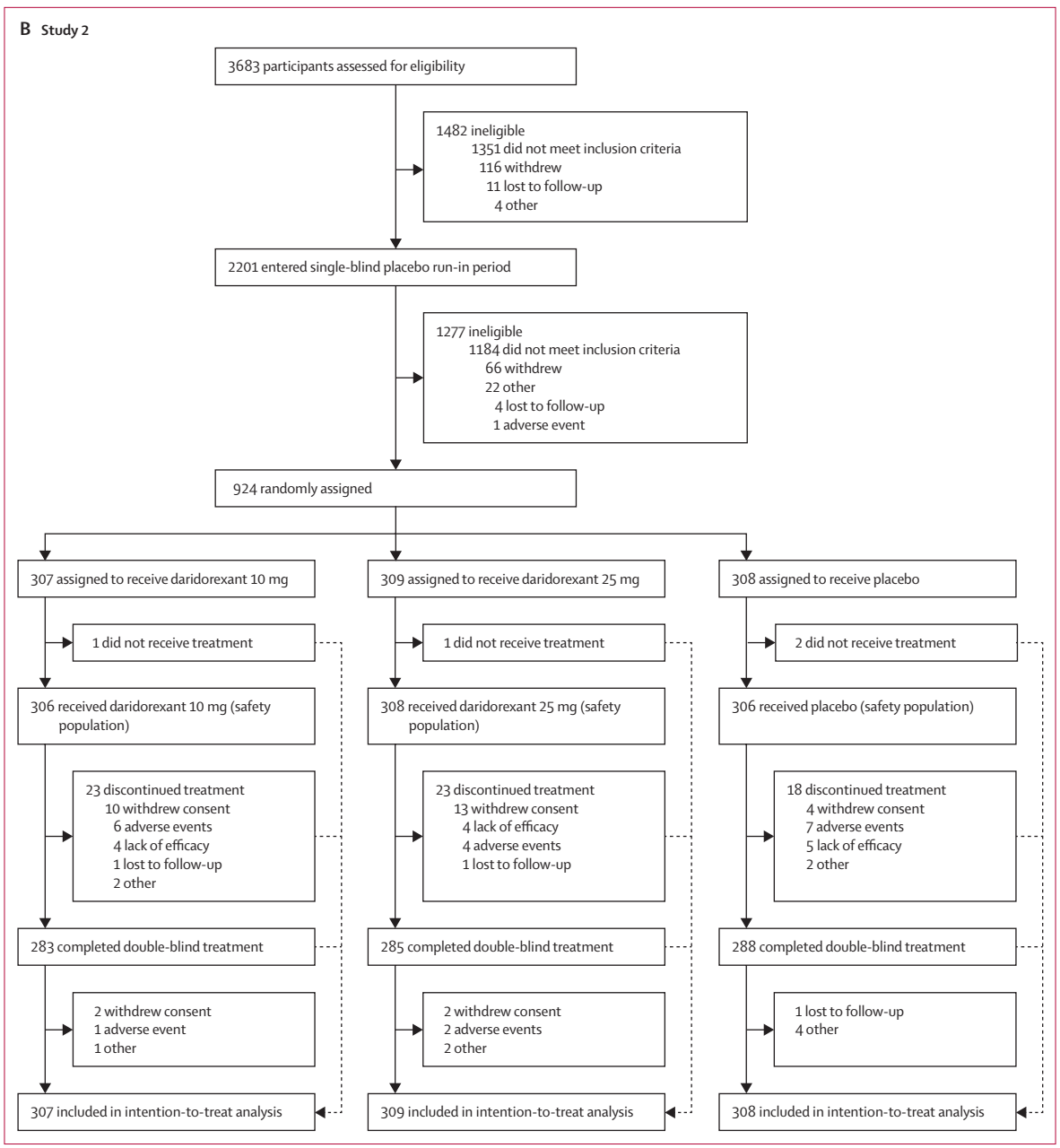


Figure 1: **Trial profiles for studies 1 and 2**

self-reported total sleep time was significantly increased compared with the placebo group at month 1 (LSM difference 16·1 min [8·2 to 24·0], p<0·0001) and month 3 (19·1 min [10·1 to 28·0], p<0·0001). Compared with placebo, no significant differences in LPS were observed at month 1 (LSM difference –6·5 min [95% CI –12·3 to –0·6], p=0·030) or month 3 (–9·0 min [–15·3 to –2·7], p=0·0053) and no significant differences in IDSIQ sleepiness domain score were observed at month 1 (LSM difference –0·8 [95% CI –1·6 to 0·1], p=0·073) or month 3 (–1·3 [–2·2 to –0·3], p=0·012). Compared with placebo, no significant differences were observed among participants in the daridorexant 10 mg group for WASO at month 1 (LSM difference –2·7 min [95% CI –8·7 to 3·2], p=0·37) or month 3 (–2·0 min [–8·7 to 4·8], p=0·57), LPS at month 1 (–2·6 min [–8·4 to 3·2], p=0·38) or month 3 (–3·2 min [–9·5 to 3·1], p=0·32), self-reported total sleep time at month 1 (13·4 min [5·5 to 21·2], p=0·0009) or month 3 (13·6 min [4·7 to 22·5], p=0·0028), or IDSIQ sleepiness domain score at month 1 (–0·4 [–1·3 to 0·4], p=0·30 or month 3 (–0·7 [–1·7 to 0·2], p=0·14; table 2, figures 2 and 3).

	Study 1			Study 2		
	Daridorexant 50 mg (n=310)	Daridorexant 25 mg (n=310)	Placebo (n=310)	Daridorexant 25 mg (n=309)	Daridorexant 10 mg (n=307)	Placebo (n=308)
Sex						
Female	199 (64%)	215 (69%)	210 (68%)	218 (71%)	215 (70%)	205 (67%)
Male	111 (36%)	95 (31%)	100 (32%)	91 (29%)	92 (30%)	103 (33%)
Age at screening, years	55·5 (15·3)	55·8 (15·3)	55·1 (15·4)	56·3 (14·4)	57·1 (14·0)	56·7 (14·1)
Age group, years						
<65	189 (61%)	189 (61%)	188 (61%)	188 (61%)	186 (61%)	187 (61%)
≥65	121 (39%)	121 (39%)	122 (39%)	121 (39%)	121 (39%)	121 (39%)
Race						
White	274 (88%)	287 (93%)	278 (90%)	271 (88%)	273 (89%)	267 (87%)
Black or African American	30 (10%)	19 (6%)	28 (9%)	26 (8%)	16 (5%)	29 (9%)
Asian	4 (1%)	3 (1%)	2 (1%)	11 (4%)	14 (5%)	10 (3%)
Other	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Geographical location						
USA	97 (31%)	99 (32%)	104 (34%)	108 (35%)	103 (34%)	114 (37%)
Non-USA	213 (69%)	211 (68%)	206 (66%)	201 (65%)	204 (66%)	194 (63%)
Body-mass index, kg/m²	26·3 (4·3)	26·6 (4·4)	26·4 (4·1)	26·1 (4·2)	26·0 (4·3)	26·2 (4·3)
<25·0	127 (41%)	122 (39%)	118 (38%)	135 (44%)	146 (48%)	135 (44%)
25·0 to ≤30	128 (41%)	125 (40%)	135 (44%)	120 (39%)	114 (37%)	119 (39%)
>30	55 (18%)	63 (20%)	57 (18%)	54 (17%)	47 (15%)	54 (18%)
Time since insomnia diagnosis, years	10·7 (10·7)	10·2 (10·1)	11·0 (10·5)	11·7 (11·9)	12·1 (12·0)	10·5 (10·5)
Night-time efficacy variables						
WASO, min	95·5 (37·8)	97·9 (38·8)	102·5 (40·8)	106·0 (49·1)	104·6 (46·2)	108·1 (48·7)
LPS, min	63·6 (37·4)	67·3 (38·6)	66·5 (39·8)	68·9 (40·5)	67·4 (41·7)	71·8 (46·1)
Self-reported total sleep time, min	313·2 (57·6)	309·8 (60·1)	315·9 (53·1)	308·5 (52·8)	308·4 (51·4)	307·6 (51·5)
Total sleep time, min	328·3 (50·2)	322·5 (55·1)	318·6 (54·4)	312·6 (68·8)	316·2 (63·5)	307·4 (69·0)
Insomnia Severity Index score	19·3 (4·0)	19·0 (4·3)	19·2 (4·0)	19·5 (4·0)	19·9 (3·8)	19·6 (4·1)
IDSIQ sleepiness domain score	22·5 (7·2)	22·1 (6·9)	22·3 (6·9)	22·2 (6·2)	22·7 (6·3)	22·6 (5·8)

Data are n (%) or mean (SD). Some percentages do not sum to 100 due to rounding. WASO=wake time after sleep onset. LPS=latency to persistent sleep. IDSIQ=Insomnia Daytime Symptoms and Impacts Questionnaire.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population (n=1854)**

Post-hoc analysis of log-transformed LPS values demonstrated that participants in the daridorexant 25 mg group in study 2 had significantly reduced LPS at months 1 and 3 (appendix p 36).

The effect of daridorexant on WASO, LPS, self-reported total sleep time, and IDSIQ sleepiness domain score was consistent in adults and older adults and across sex and geographical location (appendix pp 26–33).

In study 1, IDSIQ mood and alert/cognition domain scores and total scores at both timepoints were reduced (improved) in the daridorexant 50 mg group (all $p \leq 0{\cdot}0005$ *vs* placebo; not adjusted for multiplicity; appendix pp 34, 37). The results of the IDSIQ mood domain, alert/cognition domain, and total scores are reported in figure 3.

The empirical cumulative distribution function curves for the IDSIQ sleepiness domain for daridorexant 50 mg and 25 mg groups and placebo groups at month 1 and month 3 in study 1 are included in the appendix (p 35). The empirical cumulative distribution function curves of the observed changes from baseline at months 1 and 3 showed that the proportion of patients who achieved improvement from baseline was higher in the 50 mg group than the placebo group, with a difference in response rates of around 10–15%, depending on the threshold selected for response. Applying the responder definition of 4-point or higher within-person reduction from baseline in IDSIQ sleepiness domain score cumulative distribution yielded higher numerical response rates at both timepoints among participants in the daridorexant 50 mg group in study 1 (127 [42%] of 304 participants at month 1; 154 [53%] of 291 participants at month 3) compared with the placebo group (85 [28%] of 301 participants at month 1; 128 [44%] of 288 participants at month 3); however, no statistical comparisons were done.

Considering other efficacy and exploratory endpoints across both trials, increases in total sleep time measured by polysomnography compared with baseline were higher in the daridorexant groups than the placebo group in both studies, with the highest increase observed in the daridorexant 50 mg group, reaching an objectively

	Study 1			Study 2		
	Daridorexant 50 mg (n=310)	Daridorexant 25 mg (n=310)	Placebo (n=310)	Daridorexant 25 mg (n=309)	Daridorexant 10 mg (n=307)	Placebo (n=308)
Primary endpoints						
WASO at month 1, min						
LSM change from baseline (95% CI)	−29·0 (−32·7 to −25·3)	−18·4 (−22·1 to −14·7)	−6·2 (−9·9 to −2·5)	−24·2 (−28·5 to −19·9)	−15·3 (−19·5 to −11·1)	−12·6 (−16·8 to −8·3)
LSM difference compared with placebo (95% CI)	−22·8 (−28·0 to −17·6)	−12·2 (−17·4 to −7·0)	..	−11·6 (−17·6 to −5·6)	−2·7 (−8·7 to 3·2)	..
p value*	p<0·0001	p<0·0001	..	p=0·0001	p=0·37	..
WASO at month 3						
LSM change from baseline (95% CI)	−29·4 (−33·4 to −25·4)	−23·0 (−27·0 to −19·0)	−11·1 (−15·1 to −7·1)	−24·3 (−29·0 to −19·5)	−16·0 (−20·7 to −11·2)	−14·0 (−18·8 to −9·2)
LSM difference compared with placebo (95% CI)	−18·3 (−23·9 to −12·7)	−11·9 (−17·5 to −6·2)	..	−10·3 (−17·0 to −3·5)	−2·0 (−8·7 to 4·8)	..
p value*	p<0·0001	p<0·0001	..	p=0·0028	p=0·57	..
LPS at month 1, min						
LSM change from baseline (95% CI)	−31·2 (−34·5 to −27·9)	−28·2 (−31·5 to −24·8)	−19·9 (−23·2 to −16·5)	−26·5 (−30·6 to −22·3)	−22·6 (−26·7 to −18·5)	−20·0 (−24·1 to −15·9)
LSM difference compared with placebo (95% CI)	−11·4 (−16·0 to −6·7)	−8·3 (−13·0 to −3·6)	..	−6·5 (−12·3 to −0·6)	−2·6 (−8·4 to 3·2)	..
p value*	p<0·0001	p=0·0005	..	p=0·030	p=0·38	..
LPS at month 3						
LSM change from baseline (95% CI)	−34·8 (−38·1 to −31·5)	−30·7 (−34·0 to −27·4)	−23·1 (−26·5 to −19·8)	−28·9 (−33·4 to −24·4)	−23·1 (−27·6 to −18·6)	−19·9 (−24·4 to −15·4)
LSM difference compared with placebo (95% CI)	−11·7 (−16·3 to −7·0)	−7·6 (−12·3 to −2·9)	..	−9·0 (−15·3 to −2·7)	−3·2 (−9·5 to 3·1)	..
p value*	p<0·0001	p=0·0015	..	p=0·0053	p=0·32	..
Secondary endpoints						
sTST at month 1, min						
LSM change from baseline (95% CI)	43·6 (38·2 to 49·1)	34·2 (28·7 to 39·6)	21·6 (16·1 to 27·0)	43·8 (38·1 to 49·4)	41·0 (35·4 to 46·6)	27·6 (22·0 to 33·3)
LSM difference compared with placebo (95% CI)	22·1 (14·4 to 29·7)	12·6 (5·0 to 20·3)	..	16·1 (8·2 to 24·0)	13·4 (5·5 to 21·2)	..
p value*	p<0·0001	p=0·0013	..	p<0·0001	p=0·0009	..
sTST at month 3, min						
LSM change from baseline (95% CI)	57·7 (51·2 to 64·2)	47·8 (41·3 to 54·3)	37·9 (31·4 to 44·4)	56·2 (49·8 to 62·5)	50·7 (44·4 to 57·0)	37·1 (30·8 to 43·5)
LSM difference compared with placebo (95% CI)	19·8 (10·6 to 28·9)	9·9 (0·8 to 19·1)	..	19·1 (10·1 to 28·0)	13·6 (4·7 to 22·5)	..
p value*	p<0·0001	p=0·033	..	p<0·0001	p=0·0028	..
IDSIQ sleepiness domain score at month 1						
LSM change from baseline (95% CI)	−3·8 (−4·3 to −3·2)	−2·8 (−3·3 to −2·2)	−2·0 (−2·6 to −1·5)	−3·5 (−4·1 to −2·9)	−3·2 (−3·8 to −2·6)	−2·8 (−3·3 to −2·2)
LSM difference compared with placebo (95% CI)	−1·8 (−2·5 to −1·0)	−0·8 (−1·5 to 0·01)	..	−0·8 (−1·6 to 0·1)	−0·4 (−1·3 to 0·4)	..
p value*	p<0·0001	p=0·055	..	p=0·073	p=0·30	..
IDSIQ sleepiness domain score at month 3						
LSM change from baseline (95% CI)	−5·7 (−6·4 to −5·0)	−4·8 (−5·5 to −4·1)	−3·8 (−4·5 to −3·1)	−5·3 (−6·0 to −4·6)	−4·8 (−5·4 to −4·1)	−4·0 (−4·7 to −3·3)
LSM difference compared with placebo (95% CI)	−1·9 (−2·9 to −0·9)	−1·0 (−2·0 to 0·01)	..	−1·3 (−2·2 to −0·3)	−0·7 (−1·7 to 0·2)	..
p value*	p=0·0002	p=0·053	..	p=0·012	p=0·14	..

Thresholds for statistical significance are provided in the appendix (p 19). Mixed-effects model for repeated measures adjusted for baseline value, age group (<65; ≥65 years), treatment, timepoint, interaction of treatment by visit, and baseline by visit. IDSIQ=Insomnia Daytime Symptoms and Impacts Questionnaire. LPS=latency to persistent sleep. LSM=least squares mean. sTST=self-reported total sleep time. WASO=wake time after sleep onset. *Two-sided p value versus placebo.

Table 2: **Primary and secondary efficacy endpoints (intention-to-treat population)**

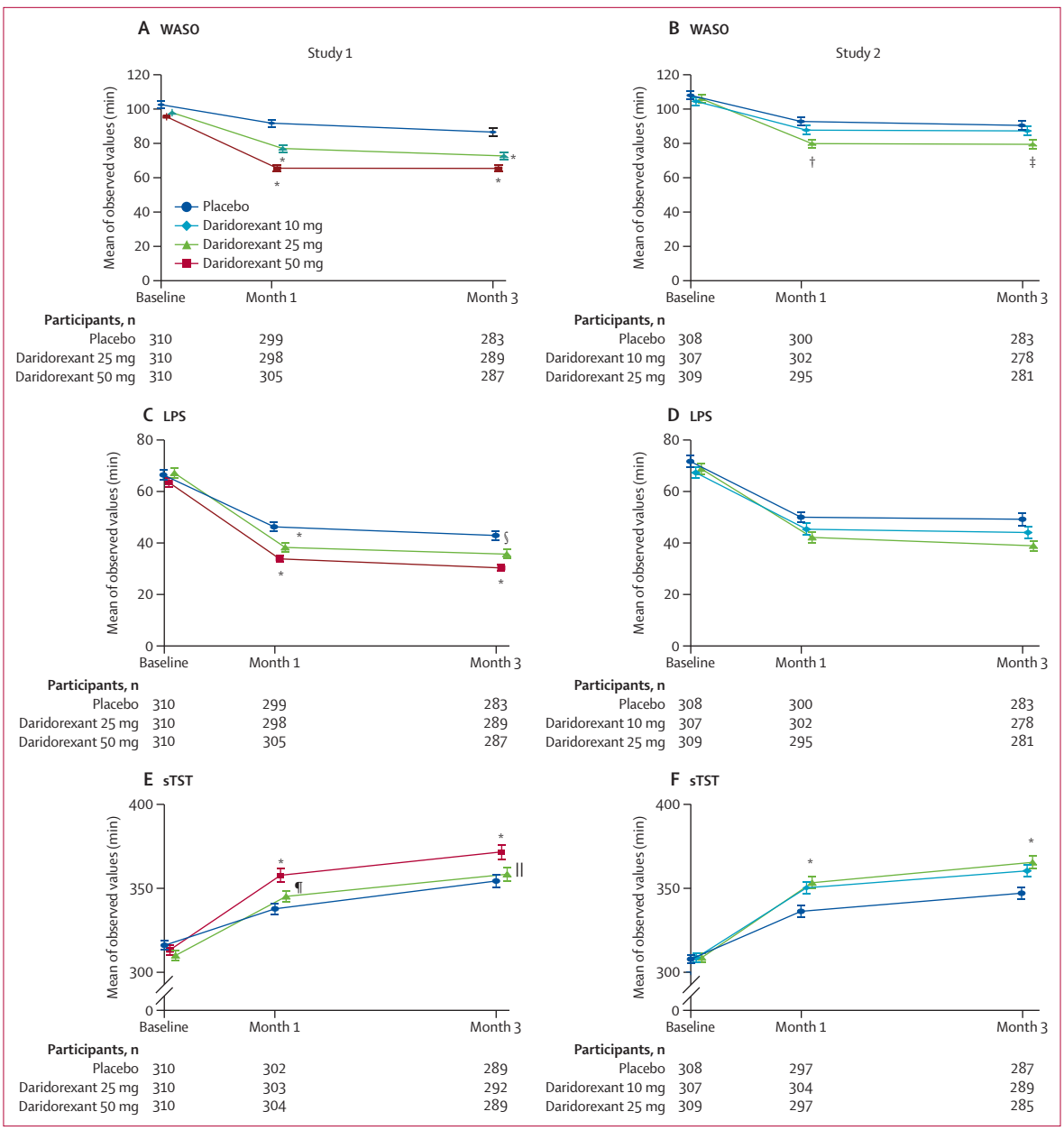
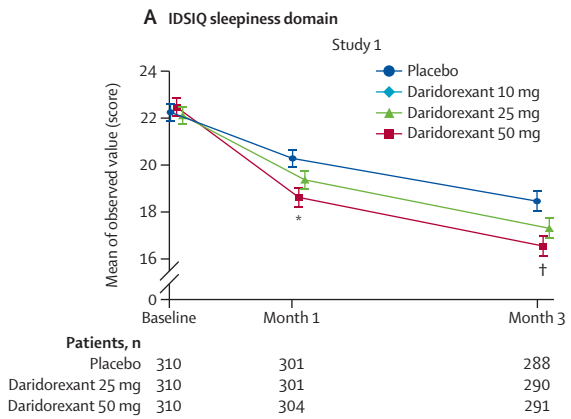
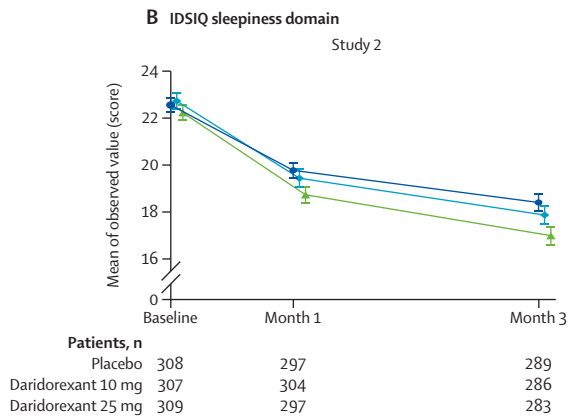


Figure 2: **Night-time efficacy endpoints**
Mean of observed WASO values at study timepoints in study 1 (A) and study 2 (B). Mean of observed LPS values at study timepoints in study 1 (C) and study 2 (D). Mean of observed sTST values at study timepoints in study 1 (E) and study 2 (F). WASO and LPS values are the mean of polysomnography recordings obtained over two consecutive nights during the 3-month double-blind treatment period. Data for sTST are based on the mean of daily entries in the 7 days before polysomnography nights. Error bars show SEM. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures. LPS=latency to persistent sleep. sTST=self-reported total sleep time. WASO=wake time after sleep onset. *p<0·0001. †p=0·0001. ‡p=0·0028. §p=0·0015. ¶p=0·0013. ||p=0·033.

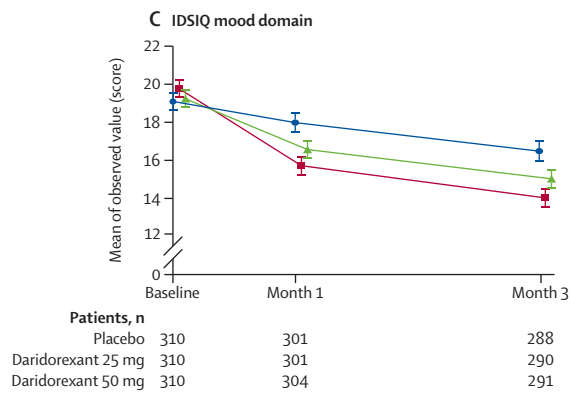
measured mean total sleep time of 6·5 h at month 3 (appendix p 39). Mean visual analogue scales scores for ability to function and daytime alertness were higher at months 1 and 3 for participants in the daridorexant groups than the placebo groups; however, this was not tested statistically (appendix p 38). The proportion of sleep time spent in each sleep stage was preserved across all treatment groups (appendix p 39), as was sleep continuity, assessed by polysomnography-measured and self-reported number of awakenings at months 1 and 3 (appendix p 40); however, no statistical comparisons were done. Visual analogue scale scores for depth and quality of sleep were numerically higher at months 1 and 3 among participants in the daridorexant groups than the placebo groups, but this was not tested statistically (appendix p 38). Insomnia Severity Index scores at



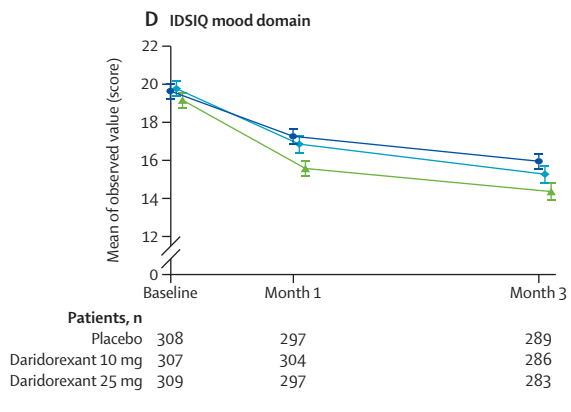
Patients, n			
Placebo	310	301	288
Daridorexant 25 mg	310	301	290
Daridorexant 50 mg	310	304	291



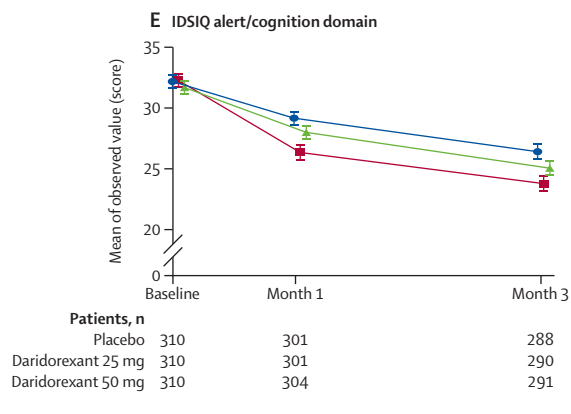
Patients, n			
Placebo	308	297	289
Daridorexant 10 mg	307	304	286
Daridorexant 25 mg	309	297	283



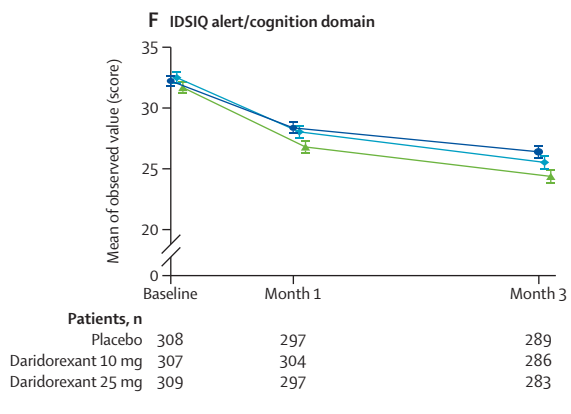
Patients, n			
Placebo	310	301	288
Daridorexant 25 mg	310	301	290
Daridorexant 50 mg	310	304	291



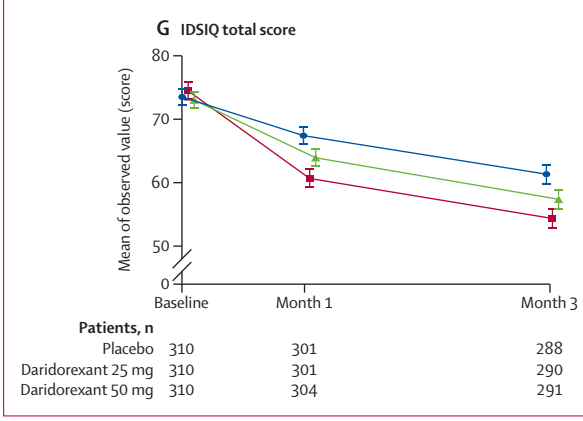
Patients, n			
Placebo	308	297	289
Daridorexant 10 mg	307	304	286
Daridorexant 25 mg	309	297	283



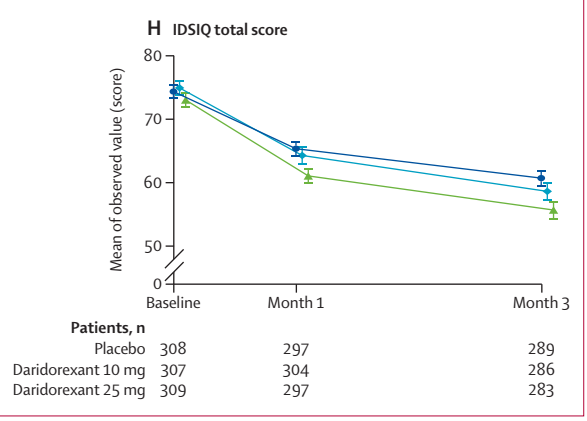
Patients, n			
Placebo	310	301	288
Daridorexant 25 mg	310	301	290
Daridorexant 50 mg	310	304	291



Patients, n			
Placebo	308	297	289
Daridorexant 10 mg	307	304	286
Daridorexant 25 mg	309	297	283



Patients, n			
Placebo	310	301	288
Daridorexant 25 mg	310	301	290
Daridorexant 50 mg	310	304	291



Patients, n			
Placebo	308	297	289
Daridorexant 10 mg	307	304	286
Daridorexant 25 mg	309	297	283

Figure 3: **IDSIQ endpoints**
Mean of observed IDSIQ sleepiness domain scores at study timepoints in study 1 (A) and study 2 (B). Mean of observed IDSIQ mood domain scores at study timepoints in study 1 (C) and study 2 (D). Mean of observed IDSIQ alert/cognition domain scores at study timepoints in study 1 (E) and study 2 (F). Mean of observed IDSIQ total scores at study timepoints in study 1 (G) and study 2 (H). IDSIQ scores are based on the mean of daily entries in the 7 days before polysomnography nights. Error bars show SEM. Two-sided p values shown are versus placebo, calculated using the linear mixed effects model for repeated measures. p values for the mood domain, alert/cognition domain, and total score comparisons versus placebo (not adjusted for multiplicity) are reported in the appendix (p 37). IDSIQ=Insomnia Daytime Symptoms and Impacts Questionnaire. *p<0·0001. †p=0·0002

	Study 1			Study 2		
	Daridorexant 50 mg (n=308)	Daridorexant 25 mg (n=310)	Placebo (n=309)	Daridorexant 25 mg (n=308)	Daridorexant 10 mg (n=306)	Placebo (n=306)
Participants with ≥1 adverse event*	116 (38%)	117 (38%)	105 (34%)	121 (39%)	117 (38%)	100 (33%)
Adverse events* leading to treatment discontinuation	3 (1%)	7 (2%)	10 (3%)	4 (1%)	6 (2%)	7 (2%)
Participants with ≥1 serious adverse event	3 (1%)	2 (1%)	7 (2%)	3 (1%)	3 (1%)	4 (1%)
Participants with adverse event* (≥2% in any group)						
Nasopharyngitis	20 (6%)	21 (7%)	20 (6%)	13 (4%)	32 (10%)	16 (5%)
Headache	19 (6%)	16 (5%)	12 (4%)	15 (5%)	12 (4%)	11 (4%)
Accidental overdose	8 (3%)	4 (1%)	5 (2%)	4 (1%)	4 (1%)	1 (<1%)
Fatigue	7 (2%)	7 (2%)	2 (1%)	11 (4%)	7 (2%)	2 (1%)
Dizziness	7 (2%)	6 (2%)	2 (1%)	6 (2%)	4 (1%)	4 (1%)
Nausea	7 (2%)	1 (<1%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)
Somnolence	5 (2%)	11 (4%)	6 (2%)	10 (3%)	6 (2%)	4 (1%)
Fall	1 (<1%)	1 (<1%)	8 (3%)	3 (1%)	4 (1%)	3 (1%)
Upper respiratory tract infection	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	6 (2%)
Adjudicated adverse events†						
Excessive daytime sleepiness	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	1 (<1%)	1 (<1%)
Sleep paralysis	1 (<1%)	1 (<1%)	0	2 (1%)	0	0
Hallucinations	0	1 (<1%)	0	1 (<1%)	0	0
Suicidal ideation or self-injury‡	0	0	0	1 (<1%)	1 (<1%)	0

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. *Adverse events that occurred during the double-blind treatment period in the safety population are included in the table and presented with their preferred terms. †Adjudicated adverse events were reported during the double-blind treatment up to 30 days after the end of treatment or date of enrolment into the extension trial and were adjudicated blindly by an independent safety board. ‡Adjudicated adverse events belonging to the category suicidal ideation or self-injury (preferred term: suicidal ideation) were reported in two participants, one in each daridorexant group in study 2; both patients had pre-existing medical conditions (paranoid schizophrenia or depression) and the independent safety board adjudicated both adverse events as potentially related to trial treatment.

Table 3: **Adverse events in the safety analysis population (n=1847)**

months 1 and 3 were numerically lower among participants in the daridorexant groups than the placebo groups in both studies, and the proportion of participants who had a decrease of 6 points or more in Insomnia Severity Index score from baseline was numerically greater at months 1 and 3 among participants given daridorexant than those given placebo; 100 (35·3%) of 310 participants in the daridorexant 50 mg group, 98 (34·3%) of 310 participants in the daridorexant 25 mg group, and 71 (25·3%) of 310 participants in the placebo group in study 1 and 95 (33·9%) of 309 participants in the daridorexant 25 mg group, 91 (33·3%) of 307 participants in the daridorexant 10 mg group, and 64 (23·1%) of 308 participants in the placebo group in study 2 had a Insomnia Severity Index score of less than 10 at month 3; however, no statistical comparisons were done (appendix p 41).

The prevalence of adverse events was similar in both trials (table 3) and was consistent across adults younger than 65 years and older adults (>65 years) in the study (appendix pp 42, 43). There was no evidence of dose dependency. Nasopharyngitis and headache were the most common adverse events in all groups. The frequency of serious adverse events was low and comparable across all treatment groups (table 3). One death (cardiac arrest) was reported in the daridorexant 25 mg group in study 1, in a participant aged 78 years with pre-existing risk factors. This death was assessed by the investigator as not related to treatment (appendix p 44). Adverse events leading to treatment discontinuation were more common in the placebo group than the daridorexant groups in both studies (table 3).

The number of participants with independent safety board-adjudicated adverse events was low (table 3). Events associated with excessive daytime sleepiness were reported in less than 1% of participants overall (one [<1%] of 308 in the daridorexant 50 mg group, two [1%] of 310 in the daridorexant 25 mg group, and one [<1%] of 309 in the placebo group in study 1; four [1%] of 308 in the daridorexant 25 mg group, one [<1%] of 306 in the daridorexant 10 mg group, and one [<1%] of 306 in the placebo group in study 2; table 3). One participant in the daridorexant 50 mg group and one participant in the daridorexant 25 mg group in study 1 and two participants in the daridorexant 25 mg group in study 2 reported sleep paralysis, and one participant each in the daridorexant 25 mg groups reported hallucinations, but no events denoting other complex sleep behaviours were reported. No participants reported cataplexy events in either trial. Suicidal ideation was reported in study 2 in

two participants (one in each daridorexant group). In both cases, confounding factors were present at baseline (both patients had pre-existing medical conditions [paranoid schizophrenia or depression]) and the independent safety board-adjudicated both adverse events as potentially related to trial treatment.

The number of participants with dizziness, fatigue, and somnolence, which are often associated with insomnia disorder or its treatment, was low, with most of these events classified as mild (none was classified as severe; table 3). In study 1, the number of participants who reported dizziness (seven [2%] of 308 in the daridorexant 50 mg group; six [2%] of 310 in the daridorexant 25 mg group) and fatigue (seven [2%] in the daridorexant 50 mg group; seven [2%] in the daridorexant 25 mg group) was higher in the daridorexant groups than in the placebo group (two [1%] of 309 reported dizziness and two [1%] reported fatigue). The number of participants who reported somnolence was similar between the 50 mg group and the placebo group (five [2%] of 308 *vs* six [2%] of 309), whereas the number of participants who reported somnolence was higher in the 25 mg group than the placebo group (11 [4%] of 310 *vs* six [2%] of 309; table 3). In study 2, the number of participants who reported somnolence (ten [3%] of 308 in the daridorexant 25 mg group; six [2%] of 306 in the daridorexant 10 mg group) and fatigue (11 [4%] of 308; seven[2%] of 306) was higher in the daridorexant groups than the placebo group (four [1%] of 306 reported somnolence and two [1%] reported fatigue). In study 1, the number of participants who reported falls was lower in the daridorexant groups than placebo groups (one [<1%] in the daridorexant 50 mg group, one [<1%] in the daridorexant 25 mg group, and eight [3%] in the placebo group) and was balanced across treatment groups in study 2 (three [1%] in the daridorexant 25 mg group, four [1%] in the 10 mg group, and three [1·0%] in the placebo group).

Participants in the daridorexant groups had numerical improvements in visual analogue scale scores for morning sleepiness versus placebo at months 1 and 3; however, no statistical comparisons were done (appendix p 45). No adverse events suggested that drug misuse might have occurred (appendix p 46). No withdrawal symptoms were observed during the placebo run-out period, as assessed by adverse events or the BWSQ (appendix pp 47, 48). During the placebo run-out period, WASO and LPS were numerically lower, and mean self-reported total sleep time was higher than respective baseline values, indicating absence of rebound insomnia; however, no statistical comparisons were done (appendix p 49).

Discussion

These two studies provide evidence of the efficacy of daridorexant on objective sleep induction and maintenance, on patient-reported sleep quantity and quality, and (at the dose of 50 mg) on daytime functioning—as measured by the IDSIQ sleepiness domain. The highest dose (daridorexant 50 mg) was the most efficacious on night-time and daytime variables, followed by 25 mg, which showed evidence of efficacy only on sleep variables; the 10 mg dose was not efficacious. Daridorexant was well tolerated and safe at all doses.

The improvements in sleep variables seen with daridorexant included both a reduction in sleep latency and an improvement in sleep maintenance. Amplitude of effect and dose was similar in adults (<65 years) and older adults (≥65 years), and the effect size remained stable after 3 months of treatment. At month 3, daridorexant 50 mg improved sleep onset and sleep maintenance to a similar extent (by approximately 30 min from baseline), resulting in an increase in total sleep time of approximately 1 h and a mean of 6·5 h sleep. These results are in line with treatment goals for the management of chronic insomnia.[16] The improvement in sleep perceived by participants was consistent with that objectively measured by polysomnography. This concordance is in contrast with the frequent discordance between subjective and objective measures of sleep in people with insomnia.[17,18] This appropriate estimation of total sleep by the participants might reflect preservation of memory[19,20] and, perhaps the fact that with daridorexant, the proportion of time spent in different sleep stages is preserved, in contrast to findings reported with benzodiazepine receptor agonists.[19,20] Daridorexant improves sleep by inhibiting orexin, a wake promoter system, rather than by inducing global sedation. This mechanism of action might explain the preservation of a normal sleep architecture. The effects noted with daridorexant were achieved without excess next-morning sleepiness and, in contrast, were complemented by an improvement in daytime functioning.

A major medical need in people with insomnia is to reverse impaired daytime functioning, which can include physical, psychological, and mental impairments.[13] Many sleep-promoting drugs cause further deterioration in daytime functioning.[21,22] Participants in the daridorexant 50 mg group reported improvements in all aspects of daytime functioning, as assessed by the newly developed and validated IDSIQ instrument (comprising mood, alert/cognition, and sleepiness domain scores).[12] The clinical importance of the effect, as often observed with the use of a new instrument, the use of which remains to become standard, might be difficult to assess. The clinical importance of the IDSIQ instrument is corroborated by the responder analysis and, more comprehensively, illustrated by the empirical cumulative distribution function, which highlights separation between the 50 mg dose and placebo, with a difference in response rates of around 10–15%, depending on the threshold selected for response. The evening visual analogue scales, indicating improved daytime alertness

and ability to function, support these findings and show that such an improvement was perceived by participants. IDSIQ scores for all groups progressively improved during the 3 months of observation.

The progressive improvement of daytime functioning reported by participants in the daridorexant groups might be explained by the night-after-night increase in sleep induction and maintenance, without change in the proportion of time spent in each sleep stage. Additional factors might also be involved in the improvement of daytime functioning, such as the absence of next-morning residual sleepiness, even at the 50 mg dose of daridorexant. Furthermore, since daridorexant is an equipotent antagonist of orexin 1 and orexin 2 receptors, and orexin 1 receptors are expressed on noradrenergic neurons, daridorexant might inhibit the chronic sympathetic hyperactivity characteristic of insomnia,[23] and this might also contribute to the improved daytime functioning.[24] The absence of residual morning sleepiness is also consistent with the pharmacokinetic profile of daridorexant. The drug was designed to have efficacy for sleep onset and maintenance at optimally efficacious doses while avoiding relevant residual drug exposure in the morning. Approximately 80% of daridorexant is eliminated within the first 8 h of dosing and there is no relevant accumulation after repeated dosing.[9,25,26]

Daridorexant was well tolerated and safe in both adults and older adults in the study. The incidence of somnolence was low among participants in the daridorexant 50 mg group and was numerically lower than the incidence in the placebo group, perhaps as a result of better sleep during the night. Nausea, headaches, mild dizziness, and fatigue were slightly more frequent in the daridorexant groups than placebo groups, whereas the incidence of falls was slightly lower in the daridorexant groups than placebo groups. The incidence of independent safety board-adjudicated adverse events was low, and no sleepwalking or automatic behaviours or cases of cataplexy or narcolepsy were reported. In animal models and pharmacological studies, prolonged and total orexin deficiency is needed to produce symptoms of narcolepsy,[27] therefore, it is not surprising that no adverse events of narcolepsy or cataplexy were observed in the daridorexant groups.

A key strength of these two studies was the assessment of most components of insomnia, as defined in DSM-5. In the trials, not only were polysomnography-based night-time variables measured but also participant-reported subjective assessments of night and day symptoms were incorporated, with robust control for study-wise type I error for all primary and secondary endpoints. In both studies, the proportion of male and female participants was representative of the general insomnia population, and older adult participants (around 40% of the study population) were well represented. The proportion of missing data was low.

These studies also had limitations. First, participants in the trials represented a population with moderate and severe insomnia, confirmed by objective measures of poor sleep. Based on the stringent inclusion criteria, these trial populations might not be representative of the general insomnia population because their insomnia might be more severe than is generally seen in practice. For example, polysomnography is seldom performed in the clinical diagnosis of insomnia and, in practice, people often have less severe insomnia. Second, most participants who were randomly assigned were White, and the screening failure rate was slightly higher among Black individuals. Therefore, the randomly assigned participants might only partly reflect the racial and ethnic diversity in some regions of the world. Third, the number of participants who had previously received cognitive behavioural therapy for insomnia was low, despite a recommendation for this treatment approach in practice guidelines. Fourth, people with comorbidities were not included. Fifth, although self-claimed impairment of daytime functioning was required for inclusion in the study, high quantitative IDSIQ scores were not required at baseline. Since the IDSIQ instrument is novel, and used prospectively for the first time in these studies, there is still limited experience with IDSIQ. Therefore, the effects of daridorexant observed with IDSIQ cannot be benchmarked with those of any other therapeutic intervention. Finally, the 3-month duration of the studies might not have been long enough to capture the maximal or long-term effects of daridorexant.

Contributors

EM, IF, TR, CLAB, DSK, and SP were involved in study conceptualisation. DSK and SP were involved in data curation. EM, DSK, and SP were involved in formal analysis and writing of the original draft of the manuscript. EM, IF, GZ, TR, DSK, and SP were involved in methodology. IF and TR were involved in resources. DSK was involved in supervision. SP was involved in validation and visualisation. DM, IF, and GZ were trial investigators or participated in the conduct of the study. EM, DL, DSK, and SP verified the data. All authors had full access to the data, were involved with review and editing of the manuscript, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

EM reports research or clinical trial funding from Axsome, Jazz Pharmaceuticals, Avadel, Apple, Huami, Sunovion, Takeda; and consultancy fees or speaker's conference reimbursement from Idorsia, Centessa Pharmaceuticals, Jazz Pharmaceuticals, Avadel, Dreem and Takeda. DM has been a clinical investigator for Apnimed, Eisai, Idorsia Pharmaceuticals, Imbrium, Janssen, Jazz Pharmaceuticals, Merck, Sage, Takeda, and Vanda. IF reports consulting fees from Bayer, Jazz Pharmaceuticals, STADA, and Takeda during the conduct of the trial. DL reports grants from Janssen, Jazz Pharmaceuticals, Merck, Philips (Netherlands), Rhythm, Sanofi, Vanda (USA), and VitalAire International outside of the submitted work. GZ reports grants and personal fees from Idorsia Pharmaceuticals during the conduct of the trials; reports receiving a salary from Clinilabs Drug Development Corporation; being a stockholder of Clinilabs Drug Development Corporation, Home Sleep and Respiratory Care, and Sleep Disorders Institute; and reports personal fees from Eisai, Janssen, Jazz Pharmaceuticals, Purdue, and Takeda outside of the submitted work. CLAB reports consultancy fees from Bioprojet, Takeda, and Jazz Pharmaceuticals during the conduct of the trials. SP and DSK are employees of Idorsia Pharmaceuticals. TR reports consultancy fees from Eisai and Takeda during the conduct of the trials.

Data sharing

The study sponsor will receive requests for individual participant data that underlie the results reported in this article, after deidentification, from researchers who provide a methodologically sound proposal. Please direct any requests to medicalinformationus@idorsia.com. Redacted protocols for each trial are available in the appendix (pp 51, 205).

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