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# Understanding daytime functioning in insomnia: responder and correlation analyses in patients treated with daridorexant

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## Abstract

**Background** Improving daytime functioning is a key treatment goal for patients with insomnia disorder. In a phase 3 study, using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), daridorexant 50 mg significantly improved daytime functioning in adults with insomnia, as well as sleep parameters. These data are further analyzed to evaluate the clinically meaningful changes in IDSIQ scores at weekly intervals and investigate the correlation between the effects of daridorexant on daytime functioning and on sleep quality and quantity.

**Methods** Nine hundred thirty patients with insomnia randomized to daridorexant 25 mg ($n=310$), 50 mg ($n=310$) or placebo ($n=310$) for 12 weeks were analyzed, with focus on daridorexant 50 mg and placebo. Patients recorded daily their daytime functioning using the IDSIQ and their self-reported total sleep time (sTST) and sleep quality using a sleep diary questionnaire; weekly mean changes from baseline were calculated. A clinically meaningful improvement ('response') at a given week was defined as a ≥ 20-point decrease in IDSIQ total score from baseline.

**Results** Weekly responder rates increased over time in both groups but were consistently higher each week with daridorexant. Overall, 53% ($n=165/310$) of patients in the daridorexant 50 mg group perceived a response for ≥ 1 week versus 41% in the placebo group ($n=126/310$). This response, which could be achieved at any time during the 12 weeks of the study, was more often continuous on daridorexant and more often intermittent on placebo. Time-to-first response was significantly different between daridorexant and placebo (hazard ratio 1.55; 95% confidence intervals [CI] 1.22, 1.97; $p=0.0003$) with shorter time observed in daridorexant. Patient perception of the response also lasted longer on daridorexant than placebo (mean number of continuous responder weeks; 9.2 vs. 7.9 respectively). A decrease in IDSIQ total score was correlated with an increase in sTST and sleep quality and a decrease in morning sleepiness, from Week 1 onwards.

**Conclusion** Patients with insomnia are more likely to perceive a clinically meaningful improvement in their daytime functioning each week with daridorexant 50 mg than placebo. The response, which can fluctuate over time, is also perceived earlier and sustained for longer than placebo. The correlations between improved daytime functioning and improved sleep quantity and quality support the benefits of daridorexant on both the night and daytime symptoms in patients with insomnia disorder.

**Trial registration** ClinicalTrials.gov: NCT03545191.

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**Keywords** Clinically meaningful improvement, IDSIQ, Insomnia, Responders, Daytime functioning, Responder analysis, Total sleep time, Sleep quality

## Introduction

Impairment in daytime functioning, which can manifest as fatigue, sleepiness, mood disturbances, irritability, and attention and concentration deficits, constitutes an important clinical feature and diagnostic criteria of insomnia disorder (American Psychiatric Association 2013; Sateia 2014). Improving daytime functioning, in addition to improving sleep, is thus a key treatment goal. Nevertheless, research into the effect of insomnia treatments on daytime functioning has, until recently, been limited primarily due to a lack of suitable validated and specific patient-reported outcome (PRO) instruments. It is generally assumed, as also suggested by the causality statement in the diagnostic criteria for insomnia disorder (Diagnostic and Statistical Manual of Mental Disorders, firth edition [DSM-5]) (American Psychiatric Association 2013), that daytime impairment is a mere consequence of sleep disturbance. However, the relationship between quantity and quality of sleep, as perceived by patients, and impaired daytime functioning has not yet been thoroughly explored.

The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) is a PRO instrument that has been recently developed and validated, in accordance with U.S. Food and Drug Administration guidelines (US FDA 2009), to specifically measure the impact of insomnia on various aspects of daytime functioning (Hudgens et al. 2021). The IDSIQ has to date been implemented in the phase 3 clinical trial program for daridorexant, a dual orexin receptor antagonist (DORA) approved for the treatment of insomnia in adults, to investigate the effect of the drug on daytime functioning in adults with moderate and severe insomnia disorder. This includes two 12-week studies (Mignot et al. 2022) and a long-term double-blind extension study (Kunz et al. 2023). Concurrently with the IDSIQ, quantitative and qualitative sleep characteristics were also collected in a daily sleep diary. In the two 12-week randomized, placebo-controlled studies (ClinicalTrials.gov identifier NCT03545191 and NCT03575104), daridorexant (50 mg and 25 mg) significantly improved objective sleep parameters and self-reported total sleep time (sTST) at Months 1 and 3 of treatment (Mignot et al. 2022). The highest dose of 50 mg, used in one of the two trials (NCT03545191) also improved various aspects of daytime functioning assessed with the IDSIQ – patients had significantly less daytime sleepiness (a pre-specified secondary endpoint, showing significant improvement at Months 1 and 3 of treatment) and a better mood and feeling of alertness compared to placebo at both timepoints.

As part of the quantitative validation of the IDSIQ, the clinically important within-patient changes from baseline for the IDSIQ total score and the three individual IDSIQ domain scores (sleepiness, mood, alert/cognition) were determined (Hudgens et al. 2021), following the FDA guidelines (US FDA 2009), to facilitate the interpretation of the clinical meaningfulness, as perceived by the patients, of the phase 3 results. Based on the threshold defined for the sleepiness domain of the IDSIQ, an initial responder analysis of the phase 3 data indicated that a greater proportion of patients treated with daridorexant 50 mg perceived a clinically meaningful improvement in daytime sleepiness compared with placebo at Months 1 and 3 of treatment (Mignot et al. 2022). Daytime functioning is, however, a subjective experience and one that is subject to within-patient variability over time, a factor that has not been fully considered in the primary analysis of the results. Focusing on single timepoints across all patients may provide only a partial picture of how treatment efficacy initiates and evolves over time in individual patients.

The objective of the present study was to delve deeper into the responder analysis of the phase 3 study and lend greater meaning and interpretation of the IDSIQ results. This analysis was performed with greater time granularity to characterize the individual patient's weekly treatment response on overall daytime functioning, in terms of time to reach a clinically relevant response, and the magnitude, variability, and sustainability of the response. The relationship between improvement in daytime functioning and in self-reported sleep quality and quantity was also investigated.

## Methods

### Data set

This analysis uses data from the phase 3, placebo-controlled randomized study that assessed the efficacy and safety of daridorexant 50 mg in patients with insomnia disorder (ClinicalTrials.gov identifier NCT03545191). While this study also evaluated daridorexant 25 mg, results here focus on daridorexant 50 mg versus placebo; the 50 mg dose was efficacious on both nighttime and daytime variables in the main, pre-planned, type I error-controlled analysis of the study, and therefore chance has been excluded with a high degree of likelihood as an explanation for the difference between daridorexant

50 mg and placebo. Corresponding data for the 25 mg dose, which confirmed efficacy only on nighttime variables in the primary analysis, are presented for completeness in the Supplementary material. The analyses evaluate the aggregated treatment group results, as well as the response at the individual patient level. The daily recording of parameters for the entire treatment period allows these analyses to take the variability of the treatment effect over time into account. Analyses also focus on self-reported measures as these are of particular relevance given the subjective nature of insomnia disorder.

### Study design

The study was conducted between May 2018 and May 2020 in ten countries at 75 sites, in accordance with principles of the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice and local regulations. The protocol was approved by institutional review boards or independent ethics committees and all patients provided written informed consent. Full details of the study design have been reported elsewhere (Mignot et al. 2022). In brief, this phase 3, double-blind, placebo-controlled, parallel-group, clinical trial randomized patients (1:1:1) to receive oral daridorexant 50 mg, daridorexant 25 mg or placebo every evening for 12 weeks. Study treatment dose adjustments were not allowed. The completion rate for the 12-week double-blind treatment period was 91.7% ($n=853/930$) (Mignot et al. 2022). The double-blind treatment period was preceded by a screening period (7–18 days) and a single-blind, placebo run-in period (13–24 days) and followed by a 7-day single-blind, placebo run-out period.

Every evening, patients completed the IDSIQ to self-report their daytime functioning for that day (Hudgens et al. 2021). The IDSIQ was rigorously developed and validated according to FDA guidance (US FDA 2009) and demonstrated good test–retest reliability and acceptable concurrent validity and responsiveness (Hudgens et al. 2021). The IDSIQ contains 14 different items assessing perceived daytime functioning in patients with insomnia disorder with a recall period of 'today'; the questions are grouped into three domains each representing the main daytime symptoms and impacts of insomnia on sleepiness (four items), alert/cognition (six items) and mood (four items) (Hudgens et al. 2021). Each item is scored on an 11-point numerical scale (from 0 to 10) with lower scores denoting better daytime functioning. Consistent with the validation study (Hudgens et al. 2021), in order to account for day-to-day variability of the measures, the mean of seven daily IDSIQ scores were used to calculate the weekly average score during the baseline period and the 12-week treatment period, which was then used in the statistical analysis. At least two IDSIQ measurements in a given week were required for the weekly average, otherwise the average IDSIQ score was set to missing for that particular week. The average daily completion rate of the IDSIQ was over 95% during the double-blind treatment period.

Patients were also required to complete daily a sleep diary questionnaire (SDQ) throughout the trial, from screening to the end of the placebo run-out period. The daily SDQ included ten questions on the previous night's sleep that were completed every morning. Patients self-reported their total sleep time (sTST) from the previous night by answering question 9, "*In total, how long did you sleep last night?*" The accompanying instructions included, "*This should be your best estimate, based on when you went to bed and woke up, how long it took you to fall asleep, and how long you were awake. You do not need to calculate this by adding and subtracting; just give your best estimate*". Using the same approach as used in the phase 2 and 3 studies (Dauvilliers et al. 2020; Mignot et al. 2022), the daily sTST values from question 9 were used to estimate the sTST (in minutes/night) at baseline and during the 12-week treatment period.

The SDQ also included morning visual analog scales (VAS) which collected information on quality of sleep and morning sleepiness, with scores ranging from 0 to 100. Quality of sleep was assessed based on the question, "*Rate the quality of your sleep last night by marking clearly and vertically across the line below*" from "*very poor*" to "*very good*", with higher scores indicating better quality of sleep. Morning sleepiness was assessed based on the question, "*Rate the way you feel this morning by marking clearly and vertically across the line below*" from "*very sleepy*" to "*not at all sleepy*", with higher scores indicating less morning sleepiness. For these SDQ-based variables (sTST and the two VAS), the same approach as used for the IDSIQ scores was applied to calculate the weekly average scores.

The insomnia severity index (ISI) score is a seven-item measure for evaluating the severity and functional and emotional impacts of insomnia over the previous month. The score of the ISI (Morin et al. 2011) was completed by patients at baseline, at Week 4, and at Week 12. The assessment of each of the seven questions of the ISI was on a 5-point scale (0–4) measuring the patients' perceptions of their insomnia, where the composite score (ranging from 0–28 points) was obtained by summing the scores from all questions. An ISI total score of 15–21 indicates a moderate level of insomnia and a score of 22–28 indicates severe insomnia (Morin et al. 2011). A 6-point reduction in the ISI total score has been shown to represent a clinically meaningful improvement in individuals with insomnia (Yang et al. 2009).

### Study participants

All study participants that were randomized in the study are included in the analyses reported here. Full details on eligibility criteria have been previously described (Mignot et al. 2022). Study participants were aged ≥ 18 years and were selected based on meeting the criteria for insomnia disorder (according to the DSM-5) which included impaired daytime functioning (American Psychiatric Association 2013). Insufficient sleep quantity was a mandatory criterion, defined based on patients' self-reported history of the following three parameters: ≥ 30 min to fall asleep, ≥ 30 min awake during sleep time, and sTST of ≤ 6.5 h. These parameters had to be present on at least three nights per week for at least 3 months before screening and also during the placebo run-in period collected using the SDQ. The subjective sleep quantity parameters were complemented by stringent objective polysomnography (PSG)-based criteria collected from two consecutive nights in the sleep laboratory during the placebo run-in period to ensure the selection of patients with difficulties in both sleep onset and maintenance: latency to persistent sleep ≥ 20 min, wake after sleep onset ≥ 30 min and total sleep time < 7 h. The severity of insomnia disorder was assessed using the ISI; eligible patients had to have self-reported insomnia of at least moderate severity at screening (ISI ≥ 15) (Morin et al. 2011). Key exclusion criteria included a history of sleep-related breathing disorders, any sleep disorder other than insomnia, or suicide ideation/attempt, self-reported daytime napping (≥ 1 h/day ≥ 3 days/week), acute/unstable psychiatric conditions, or alcohol or drug abuse. Patients with a periodic limb movements arousal index ≥ 15/h, an apnea hypopnea index ≥ 15/h or restless legs syndrome during the PSG visit in the screening period were also excluded.

### Responder analyses

Responder analyses evaluated the proportion of patients perceiving a clinically meaningful improvement equal to, or exceeding, the within-patient change threshold (also often called the minimal clinically important difference [MCID]) for IDSIQ total score. In the original validation for the IDSIQ, the MCID in the IDSIQ total score was established as a ≥ 20-point reduction from baseline using an anchor-based approach on Patient Global Impression of Change (PGI-C) and Patient Global Assessment of Disease Severity (PGA-S) data using an interventional study of 2-week treatment duration (Hudgens et al. 2021).

Each week of the 12-week treatment period was considered a timepoint in the analysis and, for each timepoint, the responder status for each individual patient was determined. A patient was defined as a 'responder' at a given timepoint if the decrease from baseline in the IDSIQ total score at that timepoint was ≥ MCID. The number of maximal consecutive weeks a patient perceived a response for was evaluated and a patient qualified as having a sustained response if he/she was a responder for several consecutive weeks (Fig. 1). To assess independence of the results to an arbitrary number of weeks, analyses were repeated based on perceiving a response for at least 2, at least 3 and at least 4 consecutive weeks. To account for fluctuation of the responder status over time, responders were further characterized as being continuous or intermittent responders. A continuous responder was a patient who maintained their responder status at all timepoints from the first response through to the last value available (Fig. 1). An intermittent responder was a patient who had a non-response at one or more timepoints following an initial response.

Analyses were repeated using a threshold of ≥ 17-point reduction in the IDSIQ total score, which, based on a larger sample of insomnia patients over a longer period of assessment, has also been shown to be clinically meaningful (Phillips-Beyer et al. 2023). Similar responder analyses were also performed for the individual IDSIQ domain scores using established clinically meaningful within-patient change thresholds of a ≥ 4-point reduction in the sleepiness and mood domains, and a ≥ 9-point reduction from baseline in the alert/cognition domain (Hudgens et al. 2021).

### Statistical analysis

All analyses were performed using SAS 9.4 and R software (4.2.1). The analyses were based on the intention-to-treat population defined as all participants assigned (i.e., randomized) to a study treatment.

Descriptive statistics are reported as means and standard deviation (SD) or standard error of the means (SE) for quantitative variables, and frequencies and percentages for qualitative data. Unless otherwise specified, the denominator to compute percentages of responders for each weekly timepoint during the 12-week treatment period is the total number of participants in the intention-to-treat population. Therefore, participants with missing information were conservatively considered as non-responders. Absolute or cumulative percentages are displayed as specified.

Linear relationships between variables were assessed using linear regression analyses. The coefficient of correlation (R), its *p*-value and the intercept and slope of the linear regression are reported.

Weekly IDSIQ changes from baseline were analyzed using a linear mixed effects model for repeated measures. The model was adjusted for the baseline IDSIQ score, age (using the randomization stratification factor < 65 years; ≥ 65 years), treatment, week,

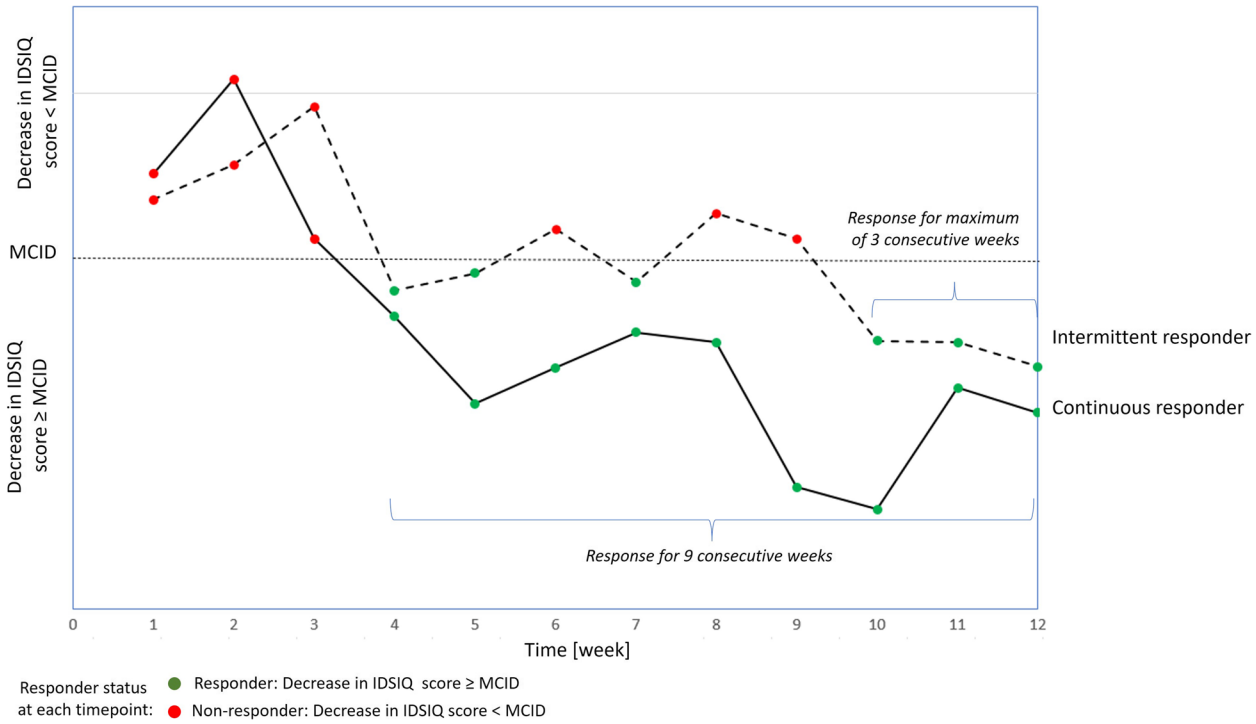



**Fig. 1** Schematic response profiles in two individual patients to illustrate the definition of continuous and intermittent responders. A participant was defined as a 'responder' at a given timepoint X if the decrease from baseline in IDSIQ total or domain score at the given timepoint was ≥ MCID. Participants could have a different responder status at different timepoints. The continuous responder as illustrated was a responder at every time point from Week 4 through to Week 12, and a non-responder at prior timepoints. The patient perceived a response for a total of nine consecutive weeks. The intermittent responder perceived a first response at Week 4 which continued to Week 5 but a non-response at Week 6, followed by further responses at Week 7, 10, 11 and 12. This patient perceived a sustained response of a maximum of three consecutive weeks from Week 10 to 12. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; MCID, minimal clinically important difference

treatment-by-week interaction and baseline-by-week interaction as fixed terms and assumed an unstructured covariance structure. For binary variables, logistic regression analysis was performed with age, treatment, week and treatment-by-week interaction as fixed terms with an unstructured covariance matrix. For both regression analyses, the three treatment groups were included in the analysis and results: e.g., least square of the means, odds ratios (ORs), are reported as point estimates and non-multiplicity adjusted 95% confidence intervals (CIs).

Time-to-first week with response (event) and time-to-first sustained response for at least 2, 3 or 4 consecutive weeks were analyzed using Kaplan–Meier analysis. The time-to-event for non-responder participants was censored at Week 12, regardless of whether they reached Week 12 or not. The difference between the cumulative incidences of the three treatment groups was assessed by a log-rank test. A proportional-hazards Cox regression analysis was also conducted to obtain an estimate of the hazard ratio (HR) between the daridorexant-treated groups versus placebo.

Two-sided $p$ values < 5% were considered statistically significant. According to the exploratory nature of these analyses, no adjustments for multiplicity were made and the $p$ values should be interpreted cautiously.

## Results

### Study population

A total of 930 patients randomly assigned to receive daridorexant 50 mg ($n = 310$), daridorexant 25 mg ($n = 310$) or placebo ($n = 310$) were included in the analysis. The majority of patients were female (67%) and White (90%) (Table 1). Overall mean age was 55.4 years with 39% of patients aged ≥ 65 years and 19% with a body mass index > 30 kg/m$^2$. Demographic and baseline characteristics were balanced between treatment groups (Mignot et al. 2022).

At baseline, there was no statistically significant correlation between the IDSIQ total score and sTST ($R = -0.056$; $p = 0.09$) (Supplementary Figure S1). Statistically significant correlations were found between IDSIQ total score and ISI score ($R = 0.527$; $p < 0.0001$), VAS quality of sleep ($R = -0.690$; $p < 0.0001$) and VAS morning

**Table 1** Baseline demographic and insomnia characteristics in the overall study group

| Characteristics | All patients *N* = 930 |
|---|---|
| Sex, n (%) | |
| Female | 624 (67%) |
| Male | 306 (33%) |
| Age at screening, years, mean (SD) | 55.4 (15.3) |
| Age group, years, n (%) | |
| ≥ 65 | 364 (39%) |
| < 65 | 566 (61%) |
| Race, n (%) | |
| White | 839 (90%) |
| Black / African American | 77 (8%) |
| Asian | 9 (1%) |
| Other | 5 (1%) |
| Geographical location, n (%) | |
| Europe | 617 (66%) |
| USA | 300 (32%) |
| Canada | 13 (1%) |
| BMI, kg/m$^2$, mean (SD) | 26.4 (4.3) |
| BMI > 30 kg/m$^2$, n (%) | 175 (19%) |
| Time since insomnia diagnosis, years, mean (SD) | 10.6 (10.4) |
| Nighttime variables, mean (SD) | |
| WASO, min[a] | 98.6 (39.2) |
| LPS, min[a] | 65.8 (38.6) |
| Total sleep time, min[a] | 323.1 (53.4) |
| Self-reported total sleep time, min | 313 (57.0) |
| Insomnia severity index score, mean (SD) (0–28)[b] | 19.1 (4.1) |
| IDSIQ total score, mean (SD) (0–140)[c] | 73.7 (24.8) |
| VAS quality of sleep, mean (SD) (0–100)[d] | 35.8 (17.5) |
| VAS morning sleepiness, mean (SD) (0–100)[d] | 37.5 (18.8) |

*BMI* body mass index, *IDSIQ* Insomnia Daytime Symptoms and Impacts Questionnaire, *LPS* latency to persistent sleep, *SD* standard deviation, *VAS* visual analog scale, *WASO* wake time after sleep onset

[a] Polysomnography values, mean of two consecutive nights

[b] higher insomnia severity index score indicates more severe insomnia

[c] lower IDSIQ total score indicates better daytime functioning

[d] higher VAS scores indicate better quality of sleep and less morning sleepiness

sleepiness ($R = -0.721$; $p < 0.0001$) at baseline (Supplementary Figure S1).

### Weekly change from baseline in IDSIQ score

The mean IDSIQ total scores decreased (i.e., improved) from baseline over time in all treatment groups (Fig. 2). Patients treated with daridorexant 50 mg had larger numerical decreases from baseline in mean IDSIQ total score than daridorexant 25 mg and placebo at each week. In the daridorexant 50 mg group, the mean (SD; n) IDSIQ total score decreased from 74.5 (25.2; 309) at baseline to 54.4 (27.4; 282) at Week 12 (mean [SD; n] change from baseline: −20.1 [23.9; 282]). In the daridorexant 25 mg group, the mean (SD; n) IDSIQ total score decreased from 73.1 (24.6; 308) at baseline to 56.6 (26.6; 274) at Week 12 (mean change −15.7 [20.8; 274]) and in the placebo group, the mean (SD; n) IDSIQ total score decreased from 73.6 (24.6; 308) to 61.5 (27.8; 276) at baseline and Week 12 respectively (mean change −12.2 [22.4; 276]).

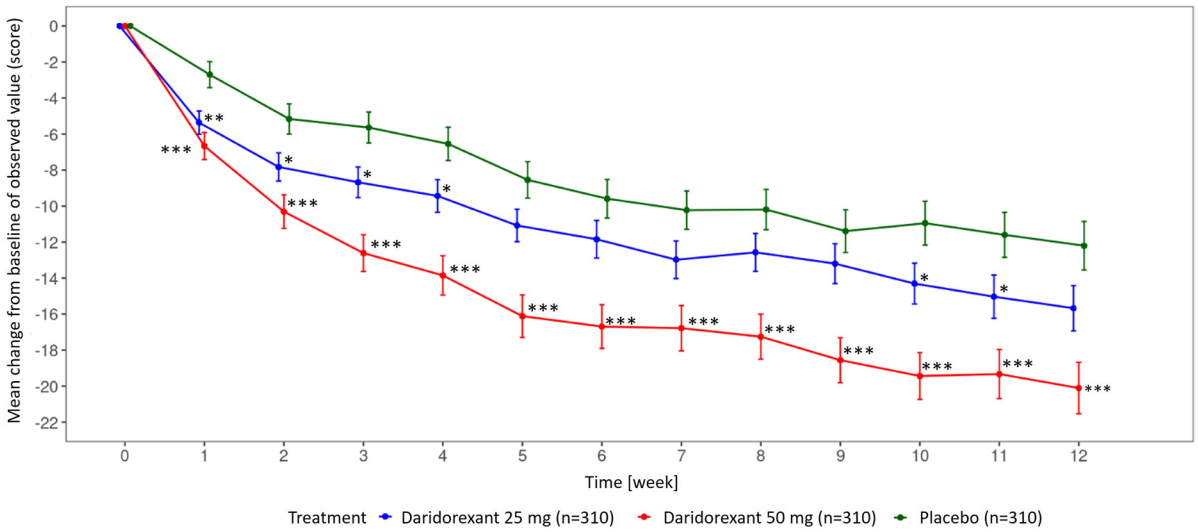
Results based on repeated measures linear regression modeling showed a statistically significant overall treatment effect on the IDSIQ total score for both doses of daridorexant versus placebo, with the largest differences reported with daridorexant 50 mg (overall mean treatment difference estimate between daridorexant 50 mg and placebo: −6.6; 95% CI −9.1, −4.1; $p < 0.0001$) (Table 2). Results for daridorexant 25 mg are summarized in Supplementary Table S1 (overall mean treatment difference estimate between daridorexant 25 mg and placebo: −2.8; 95% CI −5.3, −0.3; $p = 0.0308$).

A statistically significant treatment-by-week interaction for the IDSIQ total score was observed ($p = 0.0164$), confirming that the treatment effect varies over time. The treatment effect of daridorexant 50 mg versus placebo was statistically significant as early as Week 1 (mean treatment difference estimate −3.9 points; 95% CI −5.8, −1.9; $p < 0.0001$) and increased further up to Week 5 (−7.4 points; 95% CI −10.1, −4.6; $p < 0.0001$) (Table 2). From Week 5 through to Week 12, the treatment effect of daridorexant 50 mg versus placebo on the IDSIQ total score stabilized around a value of 7, suggesting that a plateauing had been reached. The treatment effect of daridorexant 50 mg versus placebo remained statistically significant at all timepoints (Table 2). Similar results were observed with daridorexant 25 mg, albeit to a lesser magnitude and reaching statistical significance versus placebo at only six of the 12 timepoints (Supplementary Table S1).

Results observed for the three individual IDSIQ domain scores showed a pattern similar to the results for the IDSIQ total score (Supplementary Table S2), with all questions appearing to contribute to the effect of each IDSIQ domain (Supplementary Figure S2).

### Responder analysis

The results presented here focus on the comparison between daridorexant 50 mg and placebo, using the MCID threshold of 20 points. Results for daridorexant 25 mg, which were generally intermediate between placebo and daridorexant 50 mg, and results using the MCID threshold of 17 points, which were similar to the results using the 20-point threshold, are presented




**Number of subjects**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Daridorexant 25 mg | 307 | 305 | 303 | 301 | 299 | 297 | 296 | 295 | 292 | 291 | 288 | 274 |
| Daridorexant 50 mg | 309 | 309 | 304 | 303 | 303 | 300 | 299 | 299 | 293 | 292 | 290 | 282 |
| Placebo | 306 | 303 | 301 | 301 | 300 | 297 | 297 | 297 | 291 | 291 | 291 | 276 |

**Fig. 2** IDSIQ total score over time. Mean (± SE) change from baseline in observed IDSIQ total scores over time. IDSIQ total scores are based on the mean of daily entries in the given week. Error bars show standard errors of the mean. Treatment difference between daridorexant and placebo is tested using linear regression, *p* values are reported in the graph; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p < 0.0001$ vs placebo. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; SE: standard error of the mean

**Table 2** Estimates of overall and weekly change from baseline in IDSIQ total score and treatment difference between daridorexant 50 mg versus placebo

| | **Daridorexant 50 mg** ***N*** **= 310** | **Placebo** ***N*** **= 310** | **Daridorexant 50 mg vs. Placebo** | |
|---|---|---|---|---|
| Observed baseline mean (SD) | 74.5 (25.16) | 73.6 (24.64) | – | |
| | **Change from baseline mean estimate (95% CI)** | **Change from baseline mean estimate (95% CI)** | **Treatment difference mean estimate (95% CI)** | ***P*-value** |
| Overall | −15.2 (−17.0, −13.4) | −8.6 (−10.4, −6.9) | −6.6 (−9.1, −4.1) | < 0.0001 |
| Week 1 | −6.6 (−8.0, −5.3) | −2.7 (−4.1, −1.4) | −3.9 (−5.8, −1.9) | < 0.0001 |
| Week 2 | −10.2 (−11.8, −8.6) | −5.1 (−6.7, −3.5) | −5.1 (−7.4, −2.8) | < 0.0001 |
| Week 3 | −12.3 (−14.1, −10.6) | −5.6 (−7.3, −3.8) | −6.8 (−9.2, −4.3) | < 0.0001 |
| Week 4 | −13.6 (−15.4, −11.7) | −6.5 (−8.4, −4.7) | −7.1 (−9.7, −4.5) | < 0.0001 |
| Week 5 | −15.8 (−17.8, −13.9) | −8.5 (−10.4, −6.6) | −7.4 (−10.1, −4.6) | < 0.0001 |
| Week 6 | −16.3 (−18.4, −14.3) | −9.4 (−11.5, −7.4) | −6.9 (−9.8, −4.0) | < 0.0001 |
| Week 7 | −16.3 (−18.4, −14.2) | −10.1 (−12.2, −8.0) | −6.2 (−9.2, −3.3) | < 0.0001 |
| Week 8 | −16.8 (−18.9, −14.7) | −10.1 (−12.2, −8.0) | −6.7 (−9.7, −3.7) | < 0.0001 |
| Week 9 | −17.8 (−19.9, −15.6) | −11.1 (−13.3, −9.0) | −6.6 (−9.7, −3.6) | < 0.0001 |
| Week 10 | −18.6 (−20.8, −16.4) | −10.8 (−13.0, −8.6) | −7.9 (−11.0, −4.8) | < 0.0001 |
| Week 11 | −18.4 (−20.7, −16.1) | −11.5 (−13.8, −9.2) | −6.9 (−10.2, −3.7) | < 0.0001 |
| Week 12 | −19.5 (−21.8, −17.1) | −12.1 (−14.5, −9.7) | −7.4 (−10.7, −4.0) | < 0.0001 |

*CI* confidence interval, *IDSIQ* Insomnia Daytime Symptoms and Impacts Questionnaire, *SD* standard deviation

Baseline mean (SD) corresponds to the observed IDSIQ total score at baseline. Change from baseline mean estimate, and treatment difference mean estimate (95% CI) are based on the fitted model: change from baseline IDSIQ total score = baseline weekly average score + age group + treatment + week + treatment-by-week interaction + baseline-by-week interaction

in the Supplementary material (Supplementary Figures S3-S7 and Tables S3 and S4).

#### *Response rates*

Applying the responder definition of a 20-point or higher within-patient reduction from baseline in the IDSIQ total score yielded higher response rates among patients in the daridorexant 50 mg group compared with placebo. In total, 53% ($n$ = 165/310) of patients treated with daridorexant 50 mg perceived a response at least one week, compared to 41% ($n$ =126/310) treated with placebo. After the first week of treatment, the proportion of patients perceiving a response in the daridorexant 50 mg and placebo groups was 12% and 8%, respectively (Fig. 3a). In the daridorexant 50 mg group, the proportion of responders increased sharply thereafter to reach a first fluctuating plateau at Week 5 (35%) and a second higher plateau at Week 10 (41%). In the placebo group, a plateau was reached by approximately Week 6 (27%). At all timepoints, the proportion of responders was greater in the daridorexant 50 mg group versus placebo, with most differences being statistically significant. The ORs fluctuated between 2.7 (95% CI 1.8, 4.1) at Week 3 and 1.3 (95% CI 0.9, 1.9) at Week 9 (Table 3). Overall, nine out of the 12 weekly ORs were statistically significantly greater than 1.

The responder analyses based on the three domain scores of IDSIQ were consistent with the results from the analysis of the total IDSIQ scores (Supplementary Table S3). Applying the alternative MCID of 17 points yielded higher response rates in both daridorexant 50 mg and placebo groups, with the treatment difference between the groups overall unaffected (Supplementary Table S4 and Figure S4).

#### *Time-to-first clinically meaningful and sustained response*

The Kaplan–Meier curve for time-to-first clinically meaningful response showed that the cumulative incidence in response was consistently higher in the daridorexant 50 mg group than in the daridorexant 25 mg and placebo groups (Fig. 4a). The log-rank test comparing the three treatments yielded a $p$-value of 0.0015 indicating that the time-to-first response curve was statistically different between treatment groups. The daridorexant 50 mg group achieved a greater incidence of responders as early as Week 1 and remained consistently higher than the placebo group for the 12 weeks. The daridorexant 50 mg vs placebo HR for time-to-first response estimated by the Cox regression analysis was 1.55 (95% CI 1.22, 1.97; $p$ = 0.0003). In the daridorexant 50 mg group, 50% of responders had perceived their first response by Week 3 compared to Week 5 for responders in the placebo group.

The analysis of the time-to-first sustained response for at least three consecutive weeks is depicted in Fig. 4b. Overall, 42% ($n$ = 130/310) of patients perceived a response that was sustained for at least 3 weeks on daridorexant 50 mg compared to 29% ($n$ = 89/310) on placebo. The cumulative incidence curve for the daridorexant 50 mg treatment group was higher than that for the placebo group, starting from Week 1 and during the entire treatment period. The log-rank test comparing the three treatments was statistically significant ($p$ = 0.0002). The daridorexant 50 mg vs placebo HR for time-to-first sustained response (Cox regression analysis) was 1.66 (95% CI 1.26, 2.19; $p$ = 0.0003). Similar results were obtained for the time to sustained response for at least 2 or 4 consecutive weeks (Supplementary Figure S5).

#### *Number of responder weeks*

Patients treated with daridorexant 50 mg perceived a response for an overall greater number of weeks than placebo-treated patients (Fig. 3b). Among those who responded, more than half (56%, $n$ = 92/165) in the daridorexant 50 mg group perceived a clinically meaningful response for at least 8 of 12 weeks, compared to 44% ($n$ = 55/126) in the placebo group. Focusing on the responders, the maximum number of consecutive responder weeks was also greater in the daridorexant 50 mg group compared with the placebo group (Fig. 3c). For example, 46% ($n$ = 76/165) of responders in the daridorexant 50 mg group perceived a clinically meaningful response for at least 8 consecutive weeks, compared to 35% ($n$ = 44/126) of responders in the placebo group, and 15% ($n$ = 24/165) and 9% ($n$ = 11/126) of responders in the respective groups perceived a response at all 12-week consecutive timepoints.

#### *Change in IDSIQ total score among responders/ non-responders*

Among responders, the mean decrease from baseline in the IDSIQ total score was numerically larger in the daridorexant 50 mg group compared to placebo at all time points (Fig. 5). The largest difference was observed at Week 6 where the IDSIQ total score decreased from baseline by a mean (SE) of −40.0 (1.43) and −31.8 (1.09) with daridorexant 50 mg vs placebo, respectively. A similar, albeit smaller, trend was observed among the non-responder patients, with larger mean decreases in IDSIQ total scores in the daridorexant 50 mg group at all time points compared with placebo.

#### *Continuous and intermittent response*

Using the more stringent responder definition of a 'continuous responder', whereby a patient had to perceive a response at every given timepoint from the first week of

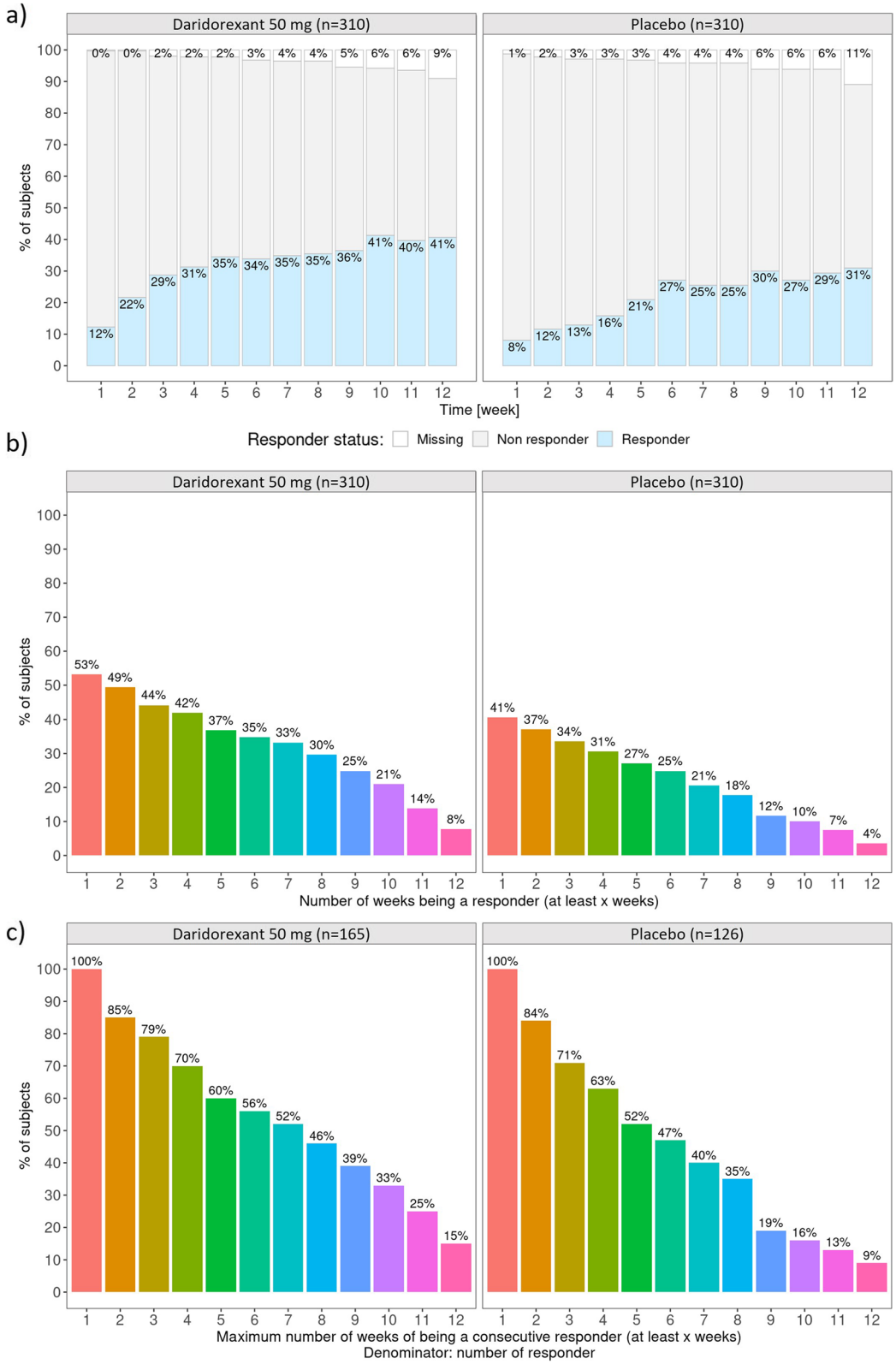



**Fig. 3** Responder analyses. The graphics show, among patients treated with daridorexant 50 mg or placebo, **a** the proportion of IDSIQ responders at each timepoint; **b** the percentage of IDSIQ responders by number of weeks with a response; **c** cumulative proportions of patients with a response over a consecutive number of weeks (maximum). A patient was defined as a 'responder' if the decrease from baseline in IDSIQ total score at a given timepoint was ≥ 20-points. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

**Table 3** Estimated odds ratios of being a responder with daridorexant 50 mg versus placebo

| | Daridorexant 50 mg vs. Placebo | |
|---|---|---|
| | **Treatment OR (95% CI)** | ***P*-value** |
| Week 1 | 1.6 (0.9, 2.7) | 0.0923 |
| Week 2 | 2.1 (1.3, 3.2) | 0.0012 |
| Week 3 | 2.7 (1.8, 4.1) | < 0.0001 |
| Week 4 | 2.4 (1.6, 3.6) | < 0.0001 |
| Week 5 | 2.0 (1.4, 2.8) | 0.0002 |
| Week 6 | 1.4 (1.0, 1.9) | 0.0773 |
| Week 7 | 1.6 (1.1, 2.2) | 0.0141 |
| Week 8 | 1.6 (1.1, 2.2) | 0.0097 |
| Week 9 | 1.3 (0.9, 1.9) | 0.1078 |
| Week 10 | 1.9 (1.4, 2.7) | 0.0002 |
| Week 11 | 1.6 (1.1, 2.2) | 0.0072 |
| Week 12 | 1.5 (1.1, 2.1) | 0.0134 |

*CI* confidence interval, *OR* odds ratio

Odds ratios of a patient achieving ≥ 20–point decrease in IDSIQ total score from baseline at a given week with daridorexant 50 mg vs placebo. Regression analysis approach: Population-averaged model. Fitted fixed factors: Age group, week, treatment group, treatment group x week interaction. Results are estimates for treatment group x week interaction fixed effect

response through to last available value, the proportion of continuous responders was numerically higher in the daridorexant 50 mg group compared with placebo.

Overall, 52% ($n=86/165$) of responders in the daridorexant 50 mg group perceived a continuous response compared with 44% ($n=56/126$) in the placebo group. The mean number of weeks a responder perceived a continuous response for was 9.2 (SD 3.18; $n=86$) weeks and 7.9 (SD 3.48; $n=56$) in the daridorexant 50 mg and placebo groups, respectively. The proportion of intermittent responders (i.e., a responder with a non-response at one or more timepoints following first response) was conversely higher in the placebo group than the daridorexant 50 mg group (56% [$n=70/126$] vs 48% [$n=79/165$] respectively). Therefore, the majority of responders in the daridorexant 50 mg group perceived a continuous response while the majority of responders receiving placebo perceived an intermittent response.

### Correlation between change from baseline in IDSIQ and in self-reported sleep parameters

During the 12-week treatment period, a reduction (i.e., improvement) in the IDSIQ total score from baseline correlated with an increase in sTST. The scatterplot for Week 12 is presented in Fig. 6a; the correlation was apparent through all weeks, with R ranging from −0.48 to −0.42 (Supplementary Figure S8). At Week 12, a decrease of 20 points in IDSIQ total score was associated with an increase in sTST of 72 min based on the linear relationship. At this timepoint, the majority of patients, 57.6%, treated with daridorexant 50 mg perceived a meaningful change in the IDSIQ total score (decrease of ≥ 20 points) and/or an increase in sTST of ≥ 72 min compared to 45.3% of patients treated with placebo; while 27.3% and 14.9% of patients in the daridorexant 50 mg and placebo groups, respectively, achieved the threshold for both outcome measures. Similar results based on the IDSIQ 17-point threshold, in which a 55-min increase in sTST corresponded to a 17-point decrease, are presented in Supplementary Figure S9.

Change from baseline in the IDSIQ total score was also inversely correlated with the change from baseline in VAS quality of sleep (Fig. 7a) and VAS morning sleepiness (Fig. 7b), in that a reduction (i.e., improvement) in IDSIQ total score was associated with an increase in both VAS scores (i.e., improvement). The correlations were apparent in all treatment groups at Week 1 and were maintained through the 12-week treatment period (Supplementary Figure S8).

For ISI, changes from baseline at the two assessed timepoints of Week 4 and Week 12 were positively correlated with changes from baseline in IDSIQ total score ($R=0.46$ [$p<0.001$] and 0.59 [$p<0.0001$], respectively) i.e., a reduction in IDSIQ total score was significantly associated with a reduction in ISI score (Fig. 6b). Based on the MCID of at least 6 points on the ISI (Yang et al. 2009), at Week 12, 61.5% of patients treated with daridorexant 50 mg achieved a clinically meaningful improvement in the IDSIQ total score and/or ISI, compared with 51.7% of patients treated with placebo; 35.2% and 22.8% of patients in the daridorexant 50 mg and placebo groups respectively achieved both clinically meaningful thresholds. Based on the correlation, at Week 12, a decrease of 20 points in IDSIQ total score corresponded to a decrease in ISI score of 8 units, which has been shown to be optimal to identify participants with marked clinical improvements (Morin et al. 2011).

Similar correlations with sTST, VAS quality of sleep, VAS morning sleepiness and ISI were observed for all three IDSIQ domains (Supplementary Figure S8).

## Discussion

This analysis indicates that mean improvement in the daytime functioning in insomnia, as measured by the IDSIQ, is time dependent and increases over time, for up to 12 weeks, in patients treated with daridorexant. While similar trends were observed in patients treated with placebo, the mean improvements in the IDSIQ total score over the 12 weeks of treatment were consistently greater, and statistically significant, with daridorexant 50 mg from as early as Week 1. The weekly responder analyses for change in IDSIQ scores showed that clinically

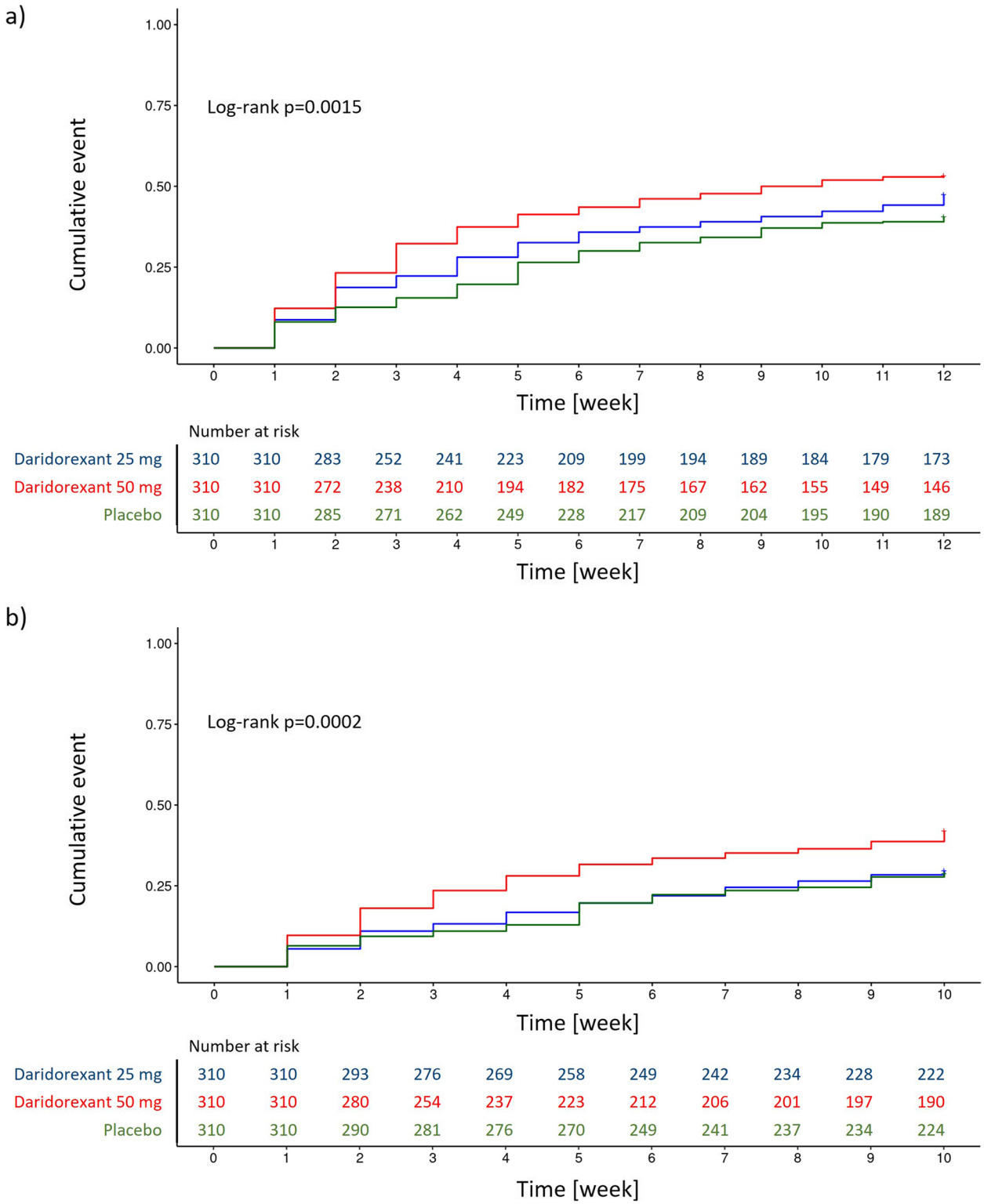



**Fig. 4** Time (weeks) to **a** first response and **b** first response sustained for at least 3 consecutive weeks. Kaplan–Meier curves showing **a** time-to-first response and **b** time-to-first sustained response for at least consecutive 3 weeks. A patient was defined as a 'responder' if decrease from baseline in IDSIQ total score at a given timepoint was ≥ 20–points. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

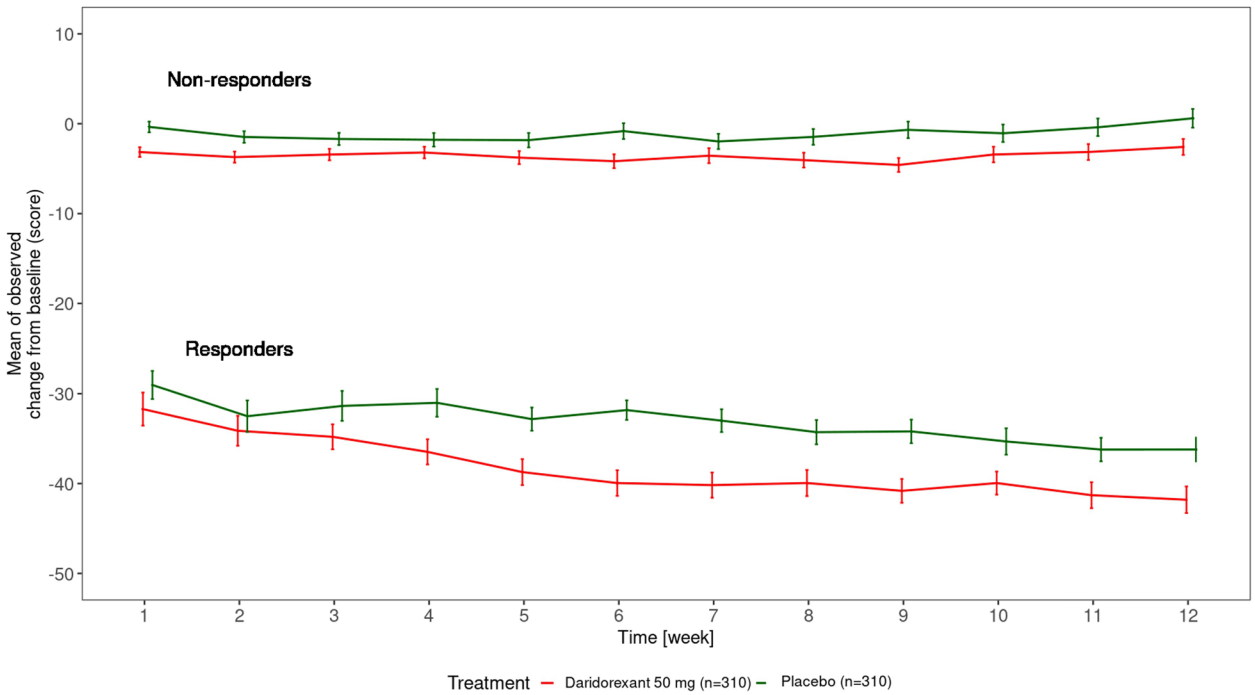


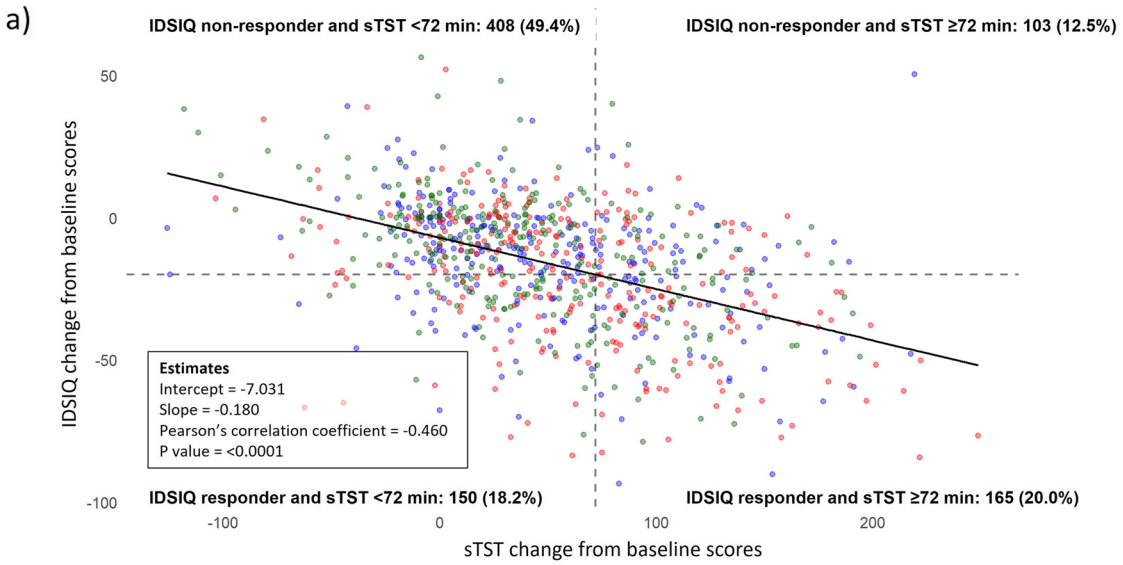

**Fig. 5** Mean change in IDSIQ total score in responders and non-responders treated with daridorexant 50 mg or placebo. Mean (± SE) change in IDSIQ total score over time in responders and non-responders receiving daridorexant 50 mg or placebo. A patient was defined as a 'responder' if decrease from baseline in IDSIQ total score at a given timepoint was ≥ 20–points. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

meaningful improvements in daytime functioning were perceived, not only by more patients treated with daridorexant than placebo each week, but also earlier, and the response was sustained for a longer period of time. The response in individual patients, irrespective of treatment, was often variable and fluctuated over time. This is not a surprise given the dynamic nature of insomnia symptoms (American Psychiatric Association 2013), although more patients perceived a continuous response in the daridorexant group as compared to placebo. This pattern of response was not identified in the more traditional analysis (Mignot et al. 2022). The results also suggest that, from the first week of treatment onward, the improvement of daytime functioning correlates strongly with perceived improvements in sleep quantity and quality and a decrease in morning sleepiness.

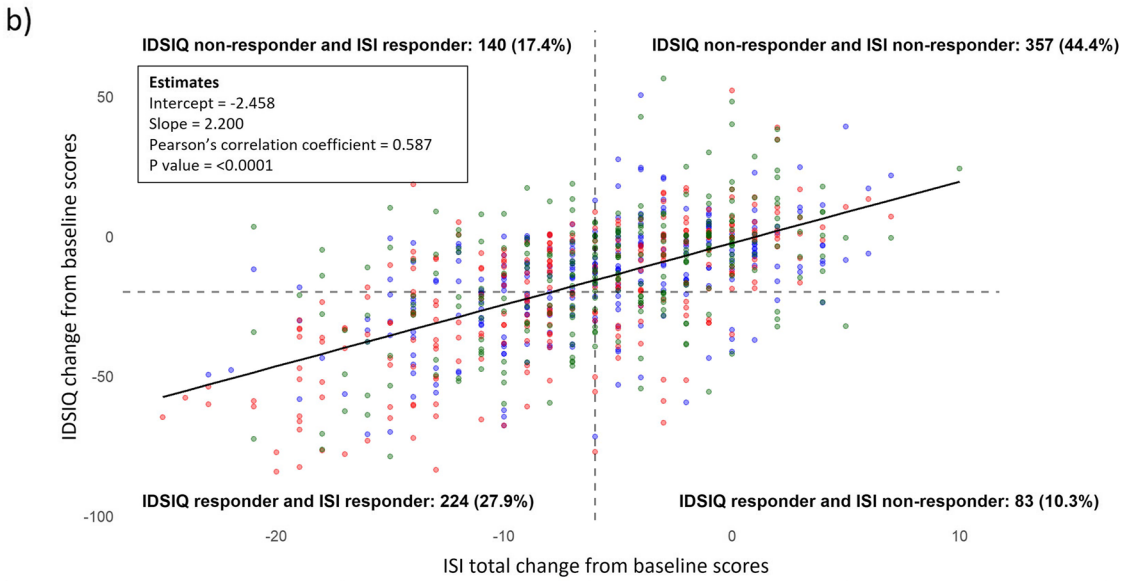
Conclusions from clinical trials are often based on mean comparisons between study groups. These are relevant to determine overall efficacy of a therapeutic intervention in a well-defined population and in a well-defined experimental condition. However, interpreting the clinical meaningfulness of the results for the group and at an individual patient level can be difficult, particularly for PRO measures such as the IDSIQ which use self-reported rating scales and which may be unfamiliar to clinicians and patients (Cappelleri et al. 2013). For this, clinicians often rely on responder analyses to characterize the meaningfulness of an individual's response

(See figure on next page.)

**Fig. 6** Correlation between change in IDSIQ total score and **a** sTST and **b** ISI at Week 12. Scatter plots showing correlation of change from baseline to Week 12 in IDSIQ total score and **a** change from baseline in sTST and **b** change from baseline in ISI total score, in patients treated with daridorexant 25 mg, daridorexant 50 mg and placebo. An IDSIQ 'responder' was defined as achieving a decrease from baseline in IDSIQ total score ≥ 20-points at a given timepoint (horizontal dashed lines). Part **a** At Week 12, a decrease of 20 points in IDSIQ total score was associated with an increase in sTST of 72 min (vertical dashed line) based on the linear relationship. The scatterplot includes the number of patients in each quadrant defined by the IDSIQ responder threshold and a threshold of 72 min for sTST. Part **b** An ISI responder was defined as achieving ≥ 6 point decrease in ISI total score (vertical dashed line). The scatterplot includes the number of patients in each quadrant of the plot defined by the IDSIQ responder threshold and a threshold of 6-points for ISI total score. The denominator in both plots is the number of participants with data available. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; ISI, insomnia severity index; sTST, self-reported total sleep time




| N (%) | Daridorexant 25 mg (n=272) | Daridorexant 50 mg (n=278) | Placebo (n=276) |
|---|---|---|---|
| IDSIQ non-responder + sTST < 72 min | 139 (51.1%) | 118 (42.4%) | 151 (54.7%) |
| IDSIQ non-responder + sTST ≥ 72 min | 39 (14.3%) | 35 (12.6%) | 29 (10.5%) |
| IDSIQ responder + sTST < 72 min | 46 (16.9%) | 49 (17.6%) | 55 (19.9%) |
| IDSIQ responder + sTST ≥ 72 min | 48 (17.6%) | 76 (27.3%) | 41 (14.9%) |
| IDSIQ responder +/or sTST ≥ 72 min | 133 (48.9%) | 160 (57.6%) | 125 (45.3%) |




| N (%) | Daridorexant 25 mg (n=267) | Daridorexant 50 mg (n=270) | Placebo (n=267) |
|---|---|---|---|
| IDSIQ non-responder + ISI responder | 52 (19.5%) | 45 (16.7) | 43 (16.1%) |
| IDSIQ non-responder + ISI non-responder | 124 (46.4%) | 104 (38.5%) | 129 (48.3%) |
| IDSIQ responder + ISI responder | 68 (25.5%) | 95 (35.2%) | 61 (22.8%) |
| IDSIQ responder + ISI non-responder | 23 (8.6%) | 26 (9.6%) | 34 (12.7%) |
| IDSIQ responder +/or ISI responder | 143 (53.6%) | 166 (61.5%) | 138 (51.7%) |

**Fig. 6** (See legend on previous page.)

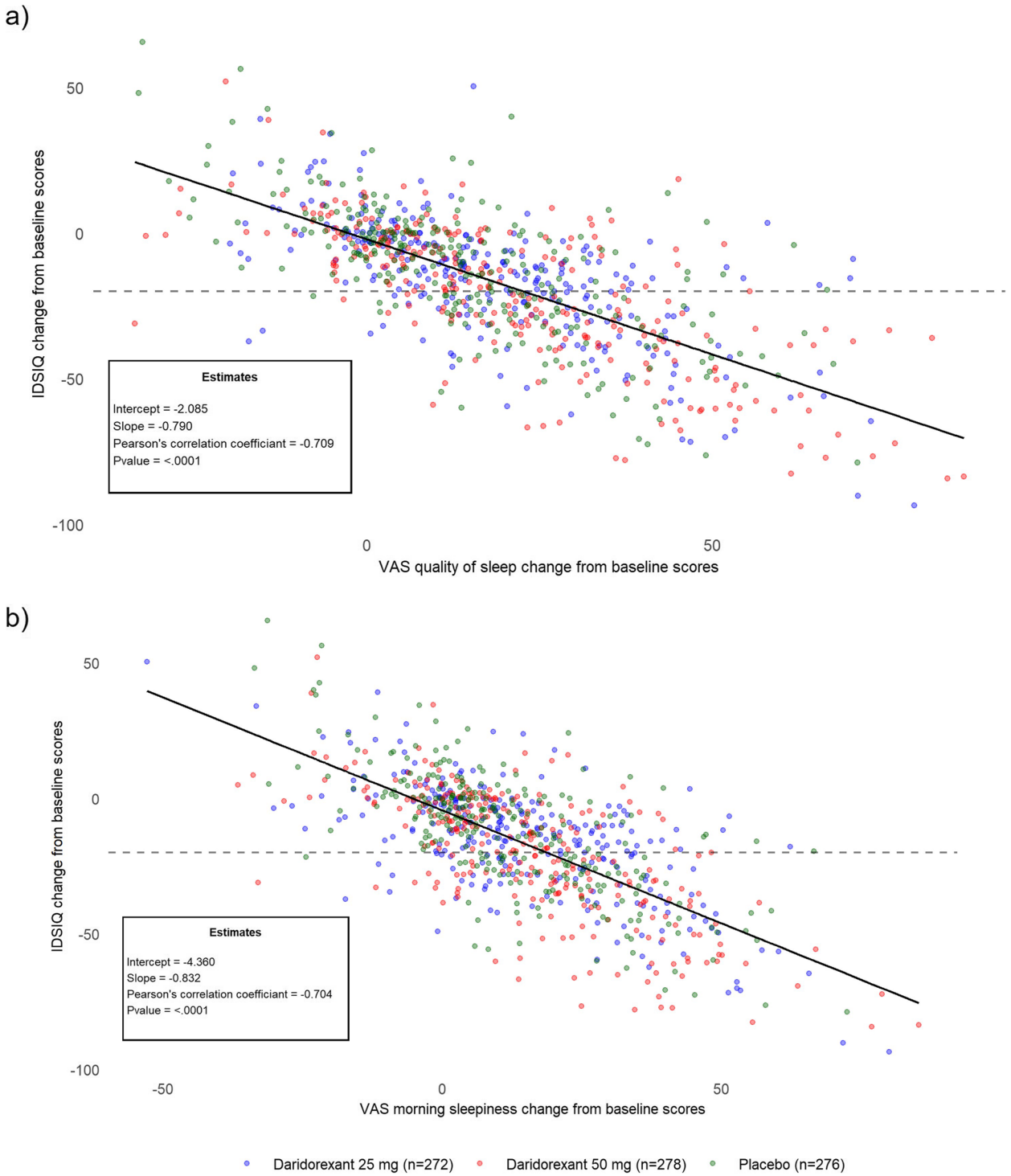



**Fig. 7** Correlation between change in IDSIQ total scores and **a** quality of sleep and **b** morning sleepiness, as assessed by VAS at Week 12. Scatter plots showing correlation of change from baseline to Week 12 in IDSIQ total score and **a** change from baseline in quality of sleep assessed by VAS and **b** change from baseline in VAS morning sleepiness, in patients treated with daridorexant 25 mg, daridorexant 50 mg and placebo. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; VAS, visual analog scale

to treatment (Guyatt et al. 1998; U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research et al. 2006). There are several difficulties in translating group mean effects into responder analyses (Atkinson et al. 2019; Cappelleri and Chambers 2021; Snapinn and Jiang 2007). First, there is a need to define what is a clinically relevant improvement on a particular outcome to facilitate the interpretation of clinical outcomes. Second, the responder status of an individual patient may vary over time and thus the determination of the response rate at a given timepoint gives an incomplete image of the true response in individuals. Third, the traditional responder analysis requires continuous outcomes, which can discriminate between varying degrees of response, to be dichotomized into a binary 'response' and 'non-response' outcome measure with consequent loss of information and specific to the defined threshold (Altman and Royston 2006). As previously discussed by Senn, a response rate of, for example, 70%, is often interpreted as 70% always-responders and 30% non-responders. However, it can also be interpreted as that the intervention works for 100% of patients for 70% of the time. From a single responder percentage, it is not possible to distinguish between these two extremes nor any scenario in between (Senn 2004). Our results, based on alternative responder analyses, contribute to this debate by demonstrating the fluctuation that can occur in a patients' individual response at different timepoints and the misinterpretation that can potentially arise if responder analyses are restricted to a single timepoint, especially in the context of insomnia symptoms fluctuating over time. In order to achieve a more accurate representation of an individual patient's treatment response, one should integrate the overall response rate with a number of other related measures, including the time-to-first response, and the magnitude, sustainability and variability of the response. Ideally, in clinical situations where the response to treatment varies over time such as in insomnia, integrating these different response characteristics into a single, holistic summary measure would provide an attractive alternative to the simpler response rate usually reported.

Insomnia is also highly sensitive to the placebo effect, which can make the detection of a treatment effect difficult (Bélanger et al. 2007). In our analyses, the placebo response rate varied according to the stringency of the response definition. However, numerical superiority of daridorexant 50 mg over placebo was detectable regardless of the responder definition and across all analyses, including multiple timepoints and all domains of daytime functioning (mood, sleepiness, alert/cognition). The findings reveal that the higher mean effect of daridorexant over placebo on daytime functioning, as identified in the pre-planned analyses (Mignot et al. 2022), is driven by a higher number of responders, a larger response among responders and an earlier and more sustained response on active therapy than placebo, and that this is true for the total score as well as the three domains that compose it. Moreover, a noteworthy observation is that, even among the patients who did not perceive a clinically meaningful change, the magnitude of perceived improvement in IDSIQ score was still greater with daridorexant 50 mg than placebo. This highlights the loss of information that can arise when an endpoint is dichotomized and the results are driven by a threshold (Altman and Royston 2006).

Insomnia is a chronic condition. Cognitive behavioral therapy is currently recommended as first-line treatment for insomnia (Qaseem et al. 2016; Riemann et al. 2017; Wilson et al. 2019). However, it is not always accessible and not all patients derive benefit, so pharmacotherapy is often the only available option. Several drugs are available for the treatment of insomnia, and most are generally recommended for short-term use (Krystal et al. 2019). The class of DORAs, in contrast, are approved for chronic use which raises the questions of how quickly do patients perceive a benefit when receiving these drugs and how sustained is this perception? Our analyses here focus on the effect of daridorexant on improving patient-reported daytime functioning, an important and often neglected characteristic of the disorder. The results highlight that improvement in daytime functioning may start early in some patients but may be more progressive in others. Furthermore, the response of an individual patient may fluctuate over time and a clinically meaningful improvement of daytime functioning may not be perceived every week as factors, other than insomnia or its treatment, may potentially impact the physical, cognitive, and psychological dimensions of their lives. It will be important for clinicians to communicate this information to patients in order to manage their expectations when using daridorexant; understanding that some patients may perceive a delayed and also variable effect on daytime impairment may encourage perseverance and adherence to a treatment plan.

We explored the relationship between self-reported daytime impairment and self-reported sleep patterns. In our analyses, prior to treatment, better daytime functioning correlated well with better quality of sleep, as well as less morning sleepiness and lower ISI total score. No correlation was observed between daytime functioning and subjectively measured quantity of sleep (i.e., sTST) at baseline. The absence of correlation between daytime impairment and sTST at baseline may be attributed, at least in part, to the inclusion criteria of $\leq$6.5 h for sTST which resulted in a truncated range of sTST data

available to estimate the correlation. During treatment, improvement in daytime functioning correlated with the improvement in all four of these self-reported measures (sTST, VAS quality of sleep, VAS morning sleepiness and ISI). We may postulate that the repetition of good quality and quantity of nighttime sleep may contribute to the improvements in daytime functioning. An additional 72 min of sleep time was associated with a 20-point decrease in IDSIQ total score from baseline (a 55-min increase corresponded to a 17-point decrease in IDSIQ total score). Although similar correlations were observed regardless of treatment arm, the greater improvements in quality and quantity of sleep observed with daridorexant 50 mg compared with placebo (Mignot et al. 2022) resulted in substantially larger benefits of daridorexant on daytime functioning. However, correlation does not imply causality. There may be product-specific properties that contribute to the improved daytime functioning seen with daridorexant and the results can not necessarily be extrapolated to other drugs, even those in the same class.

Our study has several strengths. The analyses are based on PRO measures, which are extremely relevant to insomnia due to the subjective nature of the disorder and because they directly assess the patient's status without interpretation by a clinician or anyone else. In particular, the daytime functioning was measured using a validated PRO instrument with items relevant to patients with chronic insomnia (Hudgens et al. 2021). To overcome some of the biases associated with responder analyses, we used outcome measures for which a clinically meaningful threshold has been identified (Hudgens et al. 2021; Phillips-Beyer et al. 2023). We also considered how the responder status evolved weekly over the duration of the 12-week study and took into account the sustainability of the response and the time it takes to respond, shedding some light in evaluating an effect of treatment in insomnia. The data analyzed in this report come from a well-conducted, prospective, randomized, placebo-controlled study that demonstrated the effectiveness of daridorexant in a well-characterized population of insomnia patients (Mignot et al. 2022), with large enough treatment groups. In addition, the analyses were based on the totality of the data from pre-defined endpoint yielding statistically significant results in the primary analysis of the study.

There are, however, limitations to consider when interpreting the results from these analyses. The analysis was retrospective and exploratory in nature, with no statistical adjustment on multiplicity. However, the consistency of the numerical findings and the consistently low $p$ values across all the analyses do give credibility to the robustness of the results. Given the stringent inclusion and exclusion criteria of the phase 3 study, the study population is limited to those with more moderate to severe insomnia (ISI $\geq$ 15) and considerable reduction in sleep time (sTST $\leq$ 6.5 h), which may be more severe than generally seen in the broader insomnia population. In addition, there is limited ethnic and racial diversity of the study population which may not be representative of the diversity beyond the trial. Based on published values, we used a common MCID for all patients, assuming that it is constant across severities, treatment groups and any other patient characteristics. More work may be needed to support that this is indeed the case. This analysis is based on a single trial, with no independent replication. Although we included, for completeness, the results of the 25 mg dose in the current analysis, we refrained on producing the similar analysis from the sister study of 10 mg (a non-approved dose) and 25 mg daridorexant because no statistically significant effect was identified in the primary analysis of daytime functioning in this study (Mignot et al. 2022) and therefore, we could not exclude chance as an explanation if difference had been observed in that study. Moreover, the comparison of the two doses of 25 mg and 50 mg should be made within the same study and not across studies. The fact that both studies showed a significant effect on sleep parameters of the 25 mg dose with no significant effect on daytime impairment (Mignot et al. 2022) indicates that an effect on sleep may not automatically translate into a daytime improvement. The magnitude of the effects on sleep quantity and quality may both be important to achieve an effect on daytime functioning, as the correlation results suggest, and the nighttime effects may have been insufficient with the 25 mg dose to result in daytime improvement. Therefore, the latter must be measured to make conclusion on this important insomnia characteristic. A further limitation is that while insomnia is a chronic condition, the current analysis was limited to 3 months of treatment. The analyses focused on the treatment effect of daridorexant on daytime impairment, which is extremely relevant from a patient's perspective; future analyses on the effect of daridorexant on nighttime parameters of insomnia, such as time to sleep onset and number and duration of awakenings, may be of interest in order to provide a fuller holistic assessment of the subjective responses to daridorexant. It should also be acknowledged that, in the absence of head-to-head trials comparing daridorexant to other sleep medications and in the absence of other studies utilizing the IDSIQ, no inferences about comparative efficacy are made in this paper.

## Conclusions

In conclusion, this analysis illustrates several approaches to analyze the PRO measure of daytime impairment in insomnia, complementary to the simpler analysis of mean values at given timepoints, to provide a clearer picture on the true response to treatment. The results show that not only are patients treated with daridorexant 50 mg more likely to perceive a clinically meaningful

improvement in their daytime functioning each week, they do so earlier and sustain it for longer than patients treated with placebo. Some patients treated with daridorexant may however perceive a variable and/or delayed response with regards to improving their daytime functioning, and thus managing patient expectations is important. The improvement in daytime functioning correlated with improvements in both sleep quantity and quality, thereby supporting the benefits of daridorexant in both sleep parameters as well as daytime functioning in patients with insomnia disorder.

**Abbreviations**

| | |
|---|---|
| BMI | Body mass index |
| CI | Confidence interval |
| DORA | Dual orexin receptor antagonist |
| DSM-5 | Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders |
| HR | Hazard ratio |
| IDSIQ | Insomnia Daytime Symptoms and Impacts Questionnaire |
| ISI | Insomnia severity index |
| LPS | Latency to persistent sleep |
| MCID | Minimal clinically important difference |
| OR | Odds ratio |
| PGA-S | Patient Global Assessment of Disease Severity |
| PGI-C | Patient Global Impression of Change |
| PRO | Patient-reported outcome |
| PSG | Polysomnography |
| R | Coefficient of correlation |
| SD | Standard deviation |
| SDQ | Sleep diary questionnaire |
| SE | Standard error |
| sTST | Self-reported total sleep time |
| VAS | Visual analog scale |
| WASO | Wake after sleep onset |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41606-023-00089-x.

**Additional file 1: Table S1.** Estimates of overall and weekly change from baseline in IDSIQ total score and treatment difference between daridorexant 25 mg versus placebo. **Table S2.** Estimates of overall and weekly change from baseline in IDSIQ domain scores and treatment effect versus placebo. **Table S3.** Estimated odds ratios of being a responder with daridorexant 25 mg and daridorexant 50 mg versus placebo for the individual IDSIQ domain scores. **Table S4.** Estimated odds ratios of being a responder with daridorexant 50 mg and 25 mg versus placebo using MCID 17 (IDSIQ total score). **Figure S1.** Baseline correlations between IDSIQ total score and self-reported sleep parameters. **Figure S2.** Mean change from baseline in IDSIQ item scores over time. **Figure S3.** Responder analyses with daridorexant 25 mg using MCID 20 threshold (IDSIQ total score). **Figure S4.** Responder analysis with daridorexant 50 mg, daridorexant 25 mg and placebo using MCID 17 threshold (IDSIQ total score). **Fig S5.** Time (weeks) to first sustained response defined as a) at least 2 consecutive weeks and b) at least 4 consecutive weeks using the MCID 20 threshold (IDSIQ total score). **Fig. S6.** Time (weeks) to a) first response and b) first response sustained for at least 3 consecutive weeks using the MCID 17 threshold (IDSIQ total score). **Figure S7.** Mean change in IDSIQ total score in responders and non-responders treated with daridorexant 25 mg or placebo. **Figure S8.** Weekly correlations between change in IDSIQ total and domain scores and self-reported sleep parameters. **Figure S9.** Proportion of IDSIQ responders using MCID 17 threshold (total score) and / or sTST responders at Week 12.

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**Authors' contributions**
All authors were involved in the conception and design of the analysis, interpretation of the data and drafting the first version of the manuscript. PPL was also involved in the formal analysis of the data and preparation of the figures. All authors had full access to the data, were involved with review and editing of the manuscript at each stage, approved the final version of the manuscript and had final responsibility for the decision to submit for publication and agreed to be accountable for the work.

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**Availability of data and materials**
In addition to Idorsia's existing clinical trial disclosure activities, the company is committed to implementing the Principles for Responsible Clinical Trial Data Sharing jointly issued by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA). Requests for data sharing, of any level, can be directed to clinical-trials-disclosure@idorsia.com for medical and scientific evaluation.

## Declarations

**Ethics approval and consent to participate**
The study protocol was approved by the appropriate institutional review boards or independent ethics committees and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients provided written informed consent.

**Consent for publication**
Not applicable.

**Competing interests**
All authors are employees and shareholders of Idorsia Pharmaceuticals Ltd.

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