



Dose-response of daridorexant in insomnia disorder: An analysis of Phase 2 and 3 studies

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ABSTRACT

Objective: Daridorexant is approved for the treatment of insomnia at two dose levels (25 and 50 mg). Dose-efficacy and -safety response relationships were evaluated using Phase 2 and 3 data.

Methods: Data (N = 2153) from one Phase 2 (daridorexant 5, 10, 25, 50 mg, placebo once daily for 1 month) and two Phase 3 studies (daridorexant 10 and 25 or 25 and 50 mg, placebo once daily for 3 months) were pooled. Dose-response analyses at 1 month of double-blind treatment were performed using a linear regression and a two-stage meta-analysis approach. Efficacy endpoints were polysomnography-derived wake after sleep onset, latency to persistent sleep (LPS), self-reported total sleep time and the Insomnia Daytime Symptoms and Impacts Questionnaire total score (only Phase 3 data for the latter). Safety endpoints were the incidence of total adverse events (AEs) and AEs corresponding to somnolence/fatigue.

Results: Dose-responses for all efficacy endpoints were significant in the observed dose range (both statistical approaches, $p < 0.01$). All dose-response relationships were linear except for LPS (two-stage meta-analysis) which showed a change in slope above 10 mg without reaching a plateau. No significant dose-response was observed for any AE (both approaches, $p > 0.05$). The incidence of AEs corresponding to somnolence/fatigue was low at all doses and, without linear assumption (two-stage meta-analysis) there was no dose-dependency ($p = 0.369$).

Conclusions: The data support the use of 50 mg as the preferred daridorexant dose in patients with insomnia disorder to provide the greatest opportunity for efficacy with no increased risk for AEs, including somnolence/fatigue, compared to lower doses.

1. Introduction

The determination of the most appropriate dose or dose range of a pharmacological treatment, while central to drug development, is not a straightforward exercise [1]. It requires consideration of the lowest dose that provides a discernible benefit or the maximum dose beyond which no significant further benefit is observed. It also requires the characterization of the safety profile across the dose range and consideration for individual variability [2]. The importance of “*knowing the shape and location of the population (group) average dose-response curve for both*

desirable and undesirable effects” when selecting the dose is highlighted by the International Conference on Harmonization (ICH-E4) guideline [2]. Within the development program of a drug, Phase 2 dose-finding studies play an important role in the selection of the dose range to be further considered in Phase 3. However, even when these studies have been conducted, determining the dose that gives the best benefit-risk balance can still be challenging. In fact, uncertainty related to dose selection has historically been one of the most common causes for the failure of drug applications [3]. Moreover, even after drug approval, it is not uncommon for the dose recommendation to be reduced [4].

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Identification of the optimal therapeutic dose is particularly relevant in insomnia disorder for several reasons. First, as a significant but non-lethal condition, safety remains paramount when treating patients with insomnia. Although insomnia is associated with an increased incidence of long-term adverse health outcomes [5], in the absence of evidence that hypnotic medications improve these long-term adverse outcomes, the lowest effective dose of a drug to improve sleep has historically been the rule [6]. Second, it may be difficult to distinguish between the side effects of an insomnia treatment and the manifestations of the condition itself. For example, patients may find it difficult to differentiate hypnotic-induced somnolence [7] from excessive sleepiness or fatigue, which may be common in chronic insomnia [8]. Third, although dose separation can often be achieved using pharmacodynamic biomarkers or surrogate endpoints, such as polysomnography (PSG)-derived sleep parameters, the subjective nature of insomnia necessitates the use of patient-reported outcome (PRO) instruments which may have less discriminative power [9]. Fourth, identifying a single dose that provides both optimal efficacy and safety across the spectrum of severities and heterogeneity of the patient population may be difficult. The recommended starting dose of zolpidem, a Z-drug, for example, is lower in women than men [10] and some hypnotics raise tolerability concerns in the older population who are at greater risk of falls, limiting the maximum acceptable doses [10,11].

Daridorexant is a dual orexin type 1 and 2 (OX₁ and OX₂) receptor antagonist approved for the treatment of insomnia in adults by the regulatory agencies in the US, EU, the UK, Canada and Switzerland [12]. During the development of daridorexant, single oral doses (ranging from 5 mg to 200 mg) were tested in healthy subjects in Phase 1 studies [13]. Based on the pharmacodynamic and safety assessments in these studies, doses between 5 mg and 50 mg were further investigated in patients with insomnia in two Phase 2 dose-finding studies, one in older [14] and one in younger adults [15]. In both studies, a statistically significant dose-response was characterized on the primary endpoint, PSG-determined wake after sleep onset (WASO), and no dose-response was identified on safety outcomes, suggesting that the dose of 50 mg would be adequate for further development in Phase 3 in older and younger adults with insomnia disorder. However, results on a single efficacy endpoint, WASO, may not be sufficient to determine the dose. For example, although dose-response relationships were also observed for latency to persistent sleep (LPS) and total sleep time (TST) in the Phase 2 studies, daridorexant 10 mg and 50 mg had a similar effect on LPS in elderly patients [14] and the 10 mg dose had numerically the largest effect at 4 weeks in younger adults compared to other daridorexant doses [15]. These findings suggested that a dose lower than 50 mg may be sufficient for sleep induction, with the higher dose allowing better sleep maintenance. Given the remaining uncertainty inherent to dose-finding studies run on a limited number of patients, three doses of daridorexant were included across two confirmatory Phase 3 studies, 10, 25 and 50 mg [16], to ensure best characterization of the benefit and risk across the dose range in a larger population.

Based on the results from the Phase 3 studies, the US Food and Drug Administration (FDA) approved daridorexant 50 mg and 25 mg in adults with no titration nor age or sex dose adjustment required [17]. Both doses are also approved in Europe, with daridorexant 50 mg as the recommended dose. Based on clinical judgment, some patients may be treated with 25 mg [18]. A clear dose-response has been graphically depicted based on the Phase 3 data with the highest dose studied, 50 mg, shown to have the largest effect for primary and secondary endpoints [19]. However, the dose-response relationship has not been formally investigated with respect to the complete data set collected in subjects with insomnia disorder. Here, we characterize the efficacy and safety dose-response relationship of daridorexant by combining and analyzing the data from the Phase 2 and 3 studies.

2. Methods

2.1. Data set

All Phase 2 and 3 randomized controlled trials evaluating efficacy and safety of daridorexant in patients with insomnia disorder were considered for inclusion. Only studies with available patient-level data, of parallel-design, and of at least 4 weeks treatment duration and published in peer-reviewed journals were included.

From five available studies, published in four manuscripts [14–16, 21] the analyses were conducted using data from three trials, the Phase 2 study in younger adults [15] and the two Phase 3 studies [16], each evaluating at least two doses of daridorexant within the range of 5–50 mg in patients with insomnia disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [20]. The Phase 2 study (study 201; clinicaltrials.gov: NCT02839200), a pure dose-response study, evaluated daridorexant at doses of 5 mg, 10 mg, 25 mg, and 50 mg, as well as placebo and zolpidem 10 mg [15]. The zolpidem arm was not considered in the current analysis. The two Phase 3 placebo-controlled studies investigated daridorexant at doses of 25 mg and 50 mg (study 301; NCT03575104) and 10 mg and 25 mg (study 302; NCT03545191), the data of which are published together in a single manuscript [16].

Data from the second Phase 2 study evaluating daridorexant in older adults with insomnia (NCT02841709) were not considered for these analyses due to a short treatment period of two nights only and the crossover design [14]. Data from the long-term Phase 3 extension study (study 303; NCT03679884) [21] were also not included because of the re-randomization of the placebo-treated patients to daridorexant 25 mg or placebo and the selection of a subset of patients from studies 301 and 302 based on their preference to continue in the extension phase. Data from Phase 1 studies conducted in healthy subjects were not considered due to differences in the study populations and designs.

All three studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and local regulations. Trial protocols were approved by institutional review boards or independent ethics committees as well as by national health authorities and all patients provided written informed consent.

2.2. Study design

Details of the Phase 2 and 3 studies have been published elsewhere [15,16]. In brief, study 201 was a multicenter, randomized, double-blind, placebo-controlled, active-reference, parallel-group study in which patients 18–64 years of age were randomized (1:1:1:1:1) to receive oral doses of placebo, daridorexant (5, 10, 25, or 50 mg), or zolpidem 10 mg every evening for 30 days [15]. The double-blind treatment period was preceded by a screening period (14–28 days), including two single-blind placebo nights for baseline PSG assessment, and followed by a single-blind placebo run-out for 1 day follow-up, and a 30-day safety follow-up period. The study was conducted at 38 sites in Germany, Hungary, Israel, Spain, Sweden, and the US.

The two Phase 3 studies were double-blind, placebo-controlled, parallel-group studies in which patients above 18 years of age were randomized (1:1:1) to receive oral daridorexant (study 301: 25 mg or 50 mg; study 302: 10 mg or 25 mg) or placebo every evening for 12 weeks [16]. 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) where baseline PSG assessments were done on two consecutive nights and followed by a 7-day single-blind, placebo run-out period and then either a 23-day safety follow-up or enrolment into a 40-week placebo-controlled extension study (study 303; results reported elsewhere [21]). Studies 301 and 302 were conducted in 17 countries at 156 sites, with three countries (US, Germany and Canada) contributing to both studies, but with no sites in common allowing studies to be

conducted independently. Patients had not been previously randomized in any other study involving daridorexant, including study 201. Safety and efficacy of studies 301 and 302 were monitored by an independent data monitoring committee and an independent safety monitoring board adjudicated blinded adverse events (AEs), with this latter committee also adjudicating AEs of study 201. Study treatment dose adjustments were not allowed in any of the three studies.

2.3. Study participants

Detailed inclusion/exclusion criteria have been reported elsewhere [15,16]. Eligibility criteria were overall similar across the studies, with age being the only difference between the Phase 2 and 3 studies. Study participants were aged ≥ 18 years (aged 18–64 years in the Phase 2 study) with a diagnosis of insomnia disorder (according to the DSM-5) [20] that was of at least moderate severity (Insomnia Severity Index score ≥ 15) [22]. Patients were required to have a self-reported history of disturbed sleep (≥ 30 min to fall sleep, ≥ 30 min being awake during the night and a self-reported total sleep time [sTST] of ≤ 6.5 h) on at least three nights per week for at least 3 months prior to screening. During the run-in periods, these self-reported sleep parameters were also required to be met on at least three of seven consecutive nights. During the run-in periods, PSG assessments were performed on two consecutive nights. Patients had to meet the following PSG criteria: mean of two nights WASO ≥ 30 min, LPS ≥ 30 min in study 201 and ≥ 20 min in studies 301/302, and TST < 7 h. Key exclusion criteria included a history of sleep-related breathing disorder, any sleep disorder other than insomnia, suicide ideation/attempt, self-reported daytime napping (≥ 1 h/day ≥ 3 days/week), or alcohol or drug abuse.

2.4. Endpoints

From the assessments performed in the studies, for this analysis, endpoints were selected that complementarily address efficacy on nighttime symptoms, objectively (by PSG) and subjectively (by PRO instruments), and daytime symptoms (by PRO instruments). Safety endpoints focused on treatment-emergent AEs occurring during the double-blind study period and more specifically AEs corresponding to somnolence or fatigue, based on FDA MedDRA queries (Appendix, Table A1) [23]. To account for the shorter 1-month follow-up period of study 201, the main analyses were performed on data collected during the first month of the double-blind treatment period of each study. Efficacy and safety analyses of 3-month data from the two Phase 3 studies are also reported in Appendix A.

In study 201, PSG assessments were performed on the two consecutive single-blind placebo nights at baseline, then on Days 1 and 2, 15 and 16, and 28 and 29 (Month 1) during the double-blind treatment period. In studies 301 and 302, PSG assessments were performed on two consecutive nights during the single-blind placebo baseline period, and on double-blind treatment at Month 1 (Day 27 and 28) and Month 3 (Day 83 and 84). PSG measures considered in this analysis were WASO and LPS. WASO was the primary endpoint in study 201 [15]. In studies 301 and 302, WASO and LPS were both primary endpoints [16]. The mean of the two PSG nights at each timepoint was used for the analyses.

In the three studies, using a sleep diary questionnaire, every morning patients self-reported their total sleep time (sTST) from the previous night by answering the question “*In total, how long did you sleep last night?*”. In studies 301 and 302, sTST was a key secondary endpoint [16]; the mean of the seven consecutive days immediately preceding the baseline or post-baseline PSG were evaluated for this analysis. In the Phase 2 study, baseline sTST was collected without placebo treatment while in the Phase 3 studies, values were recorded on single-blind placebo treatment.

In the Phase 3 studies, every evening, patients also self-reported their daytime functioning for that day using the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) [24]. The IDSIQ is a validated

instrument developed in accordance with FDA guidance for determining patient-reported outcomes [25]. 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: sleepiness (four items; this score was a key secondary endpoint in studies 301 and 302), alert/cognition (six items) and mood (four items). Each item is scored on an 11-point numerical scale (from 0 to 10) with lower scores denoting better daytime functioning. In a similar way than for sTST, 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. The IDSIQ total score at baseline and Months 1 and 3 in the study were evaluated for this analysis.

2.5. Statistical methods

Efficacy analyses were based on the intention-to-treat population, defined as all participants randomized to a study treatment. Safety analyses were performed on all participants who received at least one dose of study treatment, i.e., the safety set. Descriptive statistics are reported as means and standard deviations (SD) for quantitative variables, and frequencies and percentages for qualitative variables. Month 1 and Month 3 data were analyzed separately. All analyses were performed using R software (4.2.1) and SAS software (version 9.4).

Dose-response relationships were assessed using two complementary approaches, one based on individual patient data (IPD) and the second based on study summary of the individual patient data (i.e., aggregate data). In the IPD approach, patients’ data from the three studies were pooled. For efficacy parameters, the dose-response of the mean of the change from baseline and the responder rates were analyzed using linear and logistic regression methods, respectively. IPD analyses on safety parameters were based on prevalence of safety events using logistic regression. The models included, at minimum, the factor study, the continuous covariate dose and the baseline value of the given parameter (not applicable for safety parameters) as fixed effects. For LPS, the change from baseline values were log-transformed due to deviation from normality assumption. The model was adjusted for age if it was bringing a statistically significant improvement (i.e., $p < 0.05$) in model fits tested through a likelihood ratio test. Presence of heterogeneity in the treatment effect between studies was tested through a likelihood ratio test by adding the interaction of dose by study to the model. The interaction was kept in the final model only if there was evidence of heterogeneity between studies (i.e., $p < 0.10$). Without evidence of heterogeneity between studies, results assessing the presence of a dose-response are reported as the coefficients of regression for the dose (slope) and their p value and mean predicted values proportional to the amount of information brought by each study with corresponding 95 % confidence limits. Otherwise, the overall significance of a dose-response is tested through the likelihood ratio test and p values and mean predicted values with 95 % confidence limits are reported without estimation of the slope.

The second approach using study aggregate data was based on a two-stage meta-analysis using the R package (dosresmeta version: 2.0.1) developed by Crippa et al., [26]. It consists of modeling study-specific dose-response curves based on the absolute difference with placebo of the change from baseline or the risk ratio with placebo as reference for responder rate and safety prevalence, and their covariance matrix using a restricted cubic spline model (first stage). The estimated study-specific dose-response coefficients are then combined through a random-effects multivariate meta-analysis model (second stage). For the restricted cubic spline, three knots were defined at dose 5, 10, and 25 mg with other combinations being tested as sensitivity analyses. The null hypothesis of no relation between different doses and the outcome (i.e., no evidence of dose-response relationship) was tested by a multivariate Wald-type test. The heterogeneity across studies was tested using the Cochran’s Q-test. P values < 5 % were considered statistically significant and no correction for multiplicity was applied.

For responder rates analyses, a responder was defined as a participant with an improvement equal to or exceeding a pre-defined within-patient change threshold (often called the minimal clinically important difference [MCID]). For sTST and IDSIQ total score, an MCID of 55 min [27] and a ≥20-point reduction from baseline [24], respectively, were used. In the absence of validated MCID for WASO and LPS, a reduction from baseline of ≥20 min for WASO and ≥15 min for LPS were used.

3. Results

3.1. Study population and study heterogeneity

Overall, across the three studies, 2153 patients (study 201, n = 299 [14 %]; study 301, n = 930 [43 %]; study 302, n = 924 [43 %]) were

randomized to one of the daridorexant doses or placebo (i.e., daridorexant 0 mg) (Table 1). In total, 678 (31 %), 60 (3 %), 365 (17 %), 679 (32 %), and 371 (17 %) patients were randomized to placebo, or daridorexant 5, 10, 25 and 50 mg, respectively. Except for daridorexant 5 mg (only in study 201), all doses were included in at least two studies, with placebo and 25 mg included in all three studies.

Patient demographics and disease characteristics at baseline were similar in means and standard deviations across the three study populations (Table 2), with the exception of age and body mass index (BMI). By design, as study 201 did not include patients aged >65 years, the 201-study population was younger than that of the two Phase 3 studies (study 301 and 302) (mean age 44.9 vs 55.4–56.7 years). The Phase 2 study included a smaller percentage of patients with BMI >30 kg/m² compared to the Phase 3 studies (8 % vs 17–19 %).

Table 1
Studies and number of patients included in the dose-response analysis of daridorexant.

Study (reference)	Study design	Total patients (ITT), n	No. patients randomized to placebo or daridorexant dose (mg/day)				
			Placebo	5	10	25	50
201 (Dauvilliers et al. [15])	Multicenter, randomized, double-blind, placebo-controlled Phase 2; two single-blind placebo run-in nights, 30-day double-blind treatment period; single-blind placebo run-out period	299 ^a	60	60	58	60	61
301 (Mignot et al. [16])	Multicenter, randomized, double-blind, placebo-controlled Phase 3; single-blind placebo run-in period, 3-month double-blind treatment period; single-blind placebo run-out period	930	310	–	–	310	310
302 (Mignot et al. [16])		924	308	–	307	309	–
Total number of patients included in the analysis		2153	678	60	365	679	371

^a 60 patients randomized to zolpidem are not included in this analysis. ITT, intention-to-treat.

Table 2
Baseline demographic and insomnia characteristics of patients included in the analysis.

Characteristics	Phase 2		Phase 3		Overall
	201	301	302	All patients N = 2153	
	All patients N = 299	All patients N = 930	All patients N = 924		
Sex, n (%)					
Male	107 (36 %)	306 (33 %)	286 (31 %)	699 (32 %)	
Female	192 (64 %)	624 (67 %)	638 (69 %)	1454 (68 %)	
Age at screening, years, mean (SD)	44.9 (11.2)	55.4 (15.3)	56.7 (14.2)	54.5 (14.8)	
Age group, years, n (%)					
<65	299 (100 %)	566 (61 %)	561 (61 %)	1426 (66 %)	
≥65	na	364 (39 %)	363 (39 %)	727 (34 %)	
Race, n (%)					
White	267 (90 %)	839 (90 %)	811 (88 %)	1917 (90 %)	
Black/African American	29 (10 %)	77 (8 %)	71 (8 %)	177 (8 %)	
Asian	1 (<1 %)	9 (1 %)	35 (4 %)	45 (2 %)	
Other	2 (1 %)	5 (0.5 %)	7 (1 %)	14 (1 %)	
Geographical location, n (%)					
Europe	207 (69 %)	617 (66 %)	559 (60 %)	1383 (64 %)	
USA	89 (30 %)	300 (32 %)	352 (35 %)	714 (33 %)	
Canada	0	13 (1 %)	34 (4 %)	47 (2 %)	
Other	3 (1 %)	0	6 (1 %)	9 (<1 %)	
BMI, kg/m ² , mean (SD)	25.0 (3.2)	26.5 (4.3)	26.1 (4.3)	26.1 (4.2)	
BMI >30 kg/m ² , n (%)	24 (8 %)	175 (19 %)	155 (17 %)	354 (16 %)	
Time since insomnia diagnosis, years, mean (SD)	9.1 (7.6)	10.6 (10.4)	11.5 (11.5)	10.8 (10.6)	
Nighttime variables, mean (SD)					
WASO, min ^a	97.1 (38.3)	98.6 (39.2)	106.2 (48.0)	101.7 (43.2)	
LPS, min ^a	71.4 (40.0)	65.8 (38.6)	69.4 (42.8)	68.1 (40.7)	
Total sleep time, min ^a	319.0 (56.6)	323.1 (53.4)	312.1 (67.2)	317.8 (60.3)	
Self-reported total sleep time, min ^b	315.8 (52.5)	313 (57.0)	308.2 (51.9)	311.3 (54.3)	
Insomnia severity index score at screening, mean (SD) (0–28) ^c	21.1 (2.9)	21.0 (3.0)	21.0 (3.1)	21.0 (3.0)	
IDSIQ total score, mean (SD); n (0–140) ^d	nc	73.7 (24.8; 925)	74.2 (21.0; 920)	74.0 (23.0; 1845)	

BMI, body mass index; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; SD, standard deviation; WASO wake time after sleep onset; na, not applicable; nc, not collected.

^a Polysomnography values, mean of two consecutive nights – Phase 2: under placebo first administration, Phase 3: under placebo for at least 7 days.

^b sTST was collected during seven consecutive days immediately preceding the first PSG after randomization (Phase 2 study) or the baseline (Phase 3 studies) – Phase 2: under no treatment, Phase 3: under placebo.

^c Higher insomnia severity index score indicates more severe insomnia.

^d Lower IDSIQ total score indicates better daytime functioning.

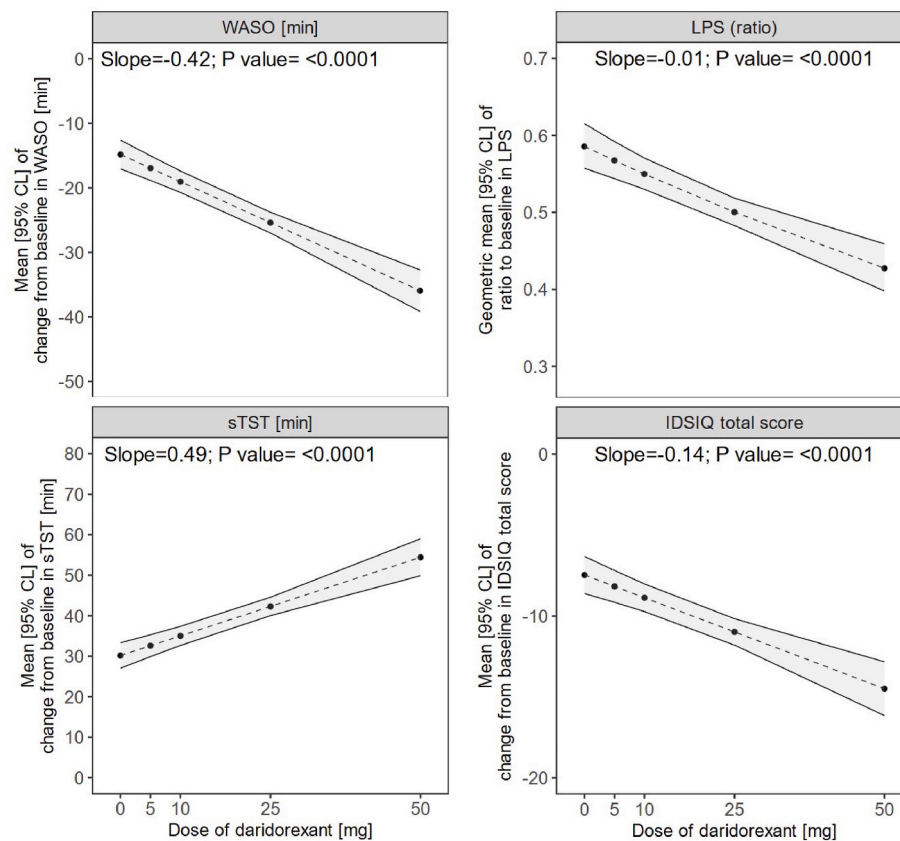


Fig. 1. IPD linear regression: modeled change from baseline in objective (WASO, LPS) and subjective (sTST, IDSIQ total score) parameters at Month 1. Modeled change from baseline [95 % confidence limit] and estimate and p value for the dose-response (slope), based on individual patient data (IPD) linear model with fixed effect approach at Month 1. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; sTST, self-reported total sleep time; WASO wake time after sleep onset.

3.2. Efficacy dose-response

The observed mean change from baseline in the four efficacy endpoints (WASO, LPS, sTST and IDSIQ total score) across the doses studied in each individual study are summarized in Appendix Table A2 and Figure A1.

3.2.1. Individual patient data (IPD) linear regression

When data from the three studies were pooled, results from the IPD linear regression confirmed a statistically significant ($p < 0.001$) linear response at Month 1 between daridorexant dose and WASO, LPS, sTST and IDSIQ total score improvement (Fig. 1). Age at screening was included in the models for WASO and sTST parameters ($p < 0.05$) and excluded for LPS ($p = 0.089$) and IDSIQ total score ($p = 0.772$). Study-by-dose interactions were not statistically significant ($p > 0.10$) in any model, providing no evidence of heterogeneity between study results, and therefore, were not included in the final linear models. Similar dose-response relationships were obtained at Month 3 on the two Phase 3 studies (Appendix Figure A2).

3.2.2. Two-stage meta-analysis

The analyses based on the two-stage meta-analysis using aggregated data (Fig. 2) also revealed statistically significant associations between dose and treatment effect for the four efficacy parameters (model $\text{Chi}^2 p < 0.01$) and there was no evidence of heterogeneity across studies (Cochran Q-test $p > 0.10$). As for the shape of the dose-response curves, improvements in WASO, sTST and IDSIQ total score from 0 mg to 50 mg were approximated by a linear response (i.e., a straight line). A change in the slope of improvement above 10 mg was observed in LPS resulting

in a non-linear shape, although without reaching a plateau. Similar dose-response relationships were again obtained at Month 3 on the two Phase 3 studies (Appendix Figure A3).

3.2.3. Responder rates

The responder rates for WASO (MCID ≤ 20 min), LPS (MCID ≤ 15 min), sTST (MCID ≥ 55 min) and IDSIQ (MCID ≤ 20 points) all showed statistically significant dose-response relationships, as confirmed with p values < 0.0001 . Similar significant dose dependency was observed using the logistic regression on IPD (Fig. 3a) and the two-stage meta-analysis (Fig. 3b). In logistic regression models, age at screening was included in the models for WASO and sTST (LPS, $p = 0.051$; IDSIQ total score, $p = 0.525$) and there was no evidence of heterogeneity between study results ($p > 0.10$).

3.3. Safety dose-response

Overall, 2146 patients (study 201, $n = 299$ [14 %]; study 301, $n = 927$ [43 %]; study 302, $n = 920$ [43 %]) received at least one dose of daridorexant or placebo during the double-blind study treatment period and were included in the safety set. This included 675 (31 %), 60 (3 %), 364 (17 %), 678 (32 %) and 369 (17 %) patients who received daridorexant 0 mg (placebo) or, daridorexant 5, 10, 25 and 50 mg respectively. The mean exposure time to study treatment during Month 1 was between 29 and 30 days. The prevalence of total AEs and AEs corresponding to somnolence or fatigue in each individual study by dose are summarized in Table 3 and Figure A.4.

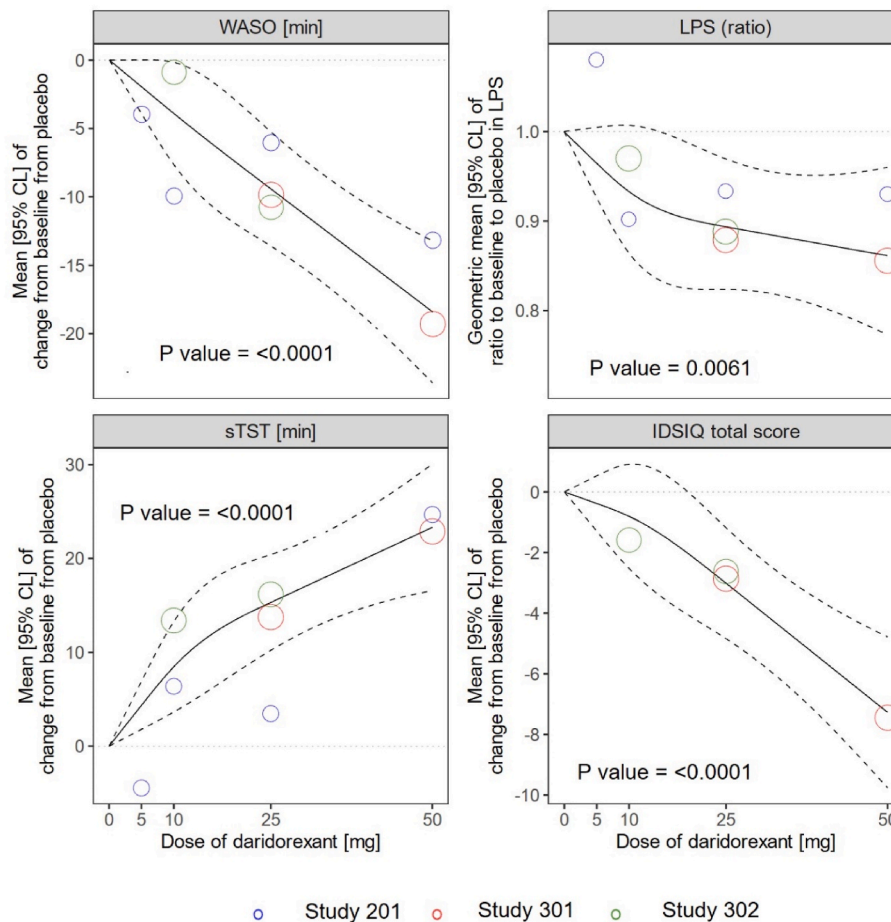


Fig. 2. Two-stage meta-analysis: modeled difference between placebo and daridorexant doses in change from baseline in objective (WASO, LPS) and subjective (sTST, IDSIQ total score) parameters at Month 1

Two-stage meta-analysis on aggregate data based on two-stage model with random-effect. The solid and dashed lines correspond to the estimation of the mean difference between placebo and daridorexant doses and associated 95 % confidence limit. The p values assess the evidence of a dose-response. The circle represents the observed value for each dose by individual study; size of the circle is proportional to the precision (inverse of variance) of the mean differences. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; LPS, latency to persistent sleep; sTST, self-reported total sleep time; WASO wake time after sleep onset.

3.3.1. IPD logistic regression

When pooling the safety data in an IPD logistic regression analysis there was no significant dose-response relationship for occurrence of any AEs during the first month ($p = 0.243$) (Fig. 3a). For AEs corresponding to somnolence/fatigue, study heterogeneity was identified ($p = 0.0376$) and the overall dose-response, assuming a linear dose-response shape, was significant ($p = 0.018$). Study 302 contributed to the heterogeneity (Appendix Figure A4), behaving differently from the two other studies, neither of which showed any significant dose dependency ($p = 0.488$). Age at screening was included in the model for somnolence/fatigue AEs. Similar safety findings were observed at Month 3, using the Phase 3 data only (Appendix Figure A.5a).

3.3.2. Two-stage meta-analysis

When relaxing the linearity assumption by performing a two-stage meta-analysis on the aggregated data of the three studies, there was no evidence of dose dependency, neither in somnolence/fatigue ($p = 0.2417$), nor in any AE ($p = 0.1436$) (Fig. 3b). In addition, there was no evidence of heterogeneity between studies (AEs $p = 0.961$; somnolence/fatigue $p = 0.369$). The modeled data showed an increase of prevalence of all AEs and AEs denoting somnolence/fatigue up to 10–25 mg followed by a plateau up to 50 mg corresponding to a saturation dose-response curve.

Analyses at Month 3 similarly showed no evidence of a dose-response in any AE ($p = 0.1266$) (Appendix Figure A5b). For AEs denoting

somnolence/fatigue, the p value was 0.0209, driven by a dose-response from 0 to 10 mg, with no increase between 25 mg and 50 mg.

3.4. Discussion

This analysis of data from three randomized placebo-controlled trials provides evidence of a dose-response relationship with daridorexant on improving objective and subjective sleep endpoints, as well as patient-reported daytime symptoms of insomnia, in the range of doses studied (5–50 mg). With regards to safety, there was a slight increase in the prevalence of AEs from dose 0 mg up to 10–25 mg, but no evidence of any significant dose-related increase in the frequency of AEs.

Identifying the optimal dosing of a drug is challenging, and failure to do so can result in suboptimal efficacy if the dose is too low, or a higher rate of AEs if the dose is unnecessarily high. The Phase 3 program of suvorexant is one example that can be used to illustrate the difficulties. It was conducted at two dose levels of 40 mg (35 mg in elderly) and 20 mg (15 mg in elderly) [28]. While the 20 mg dose was approved in an up-titration scheme, during the FDA review it was determined that a lower dose of 10 mg, a dose evaluated in Phase 2 but not tested in the confirmatory studies, should be the starting dose [6]. In the daridorexant program, by including three dose levels in Phase 3 (10 mg, 25 mg, 50 mg), a better understanding of the dose-response relationship was achieved and resulted in the two higher doses being approved, without any need for titration. In an ideal scenario, the three doses would have

been studied in the same study. Nevertheless, in our case of daridorexant, due to the similarity in study designs, data collection and population characteristics, we were able to combine the data, together with Phase 2 data, to perform a combined analysis and provide a further comprehensive and robust quantitative analysis of the dose-response

relationship. Although previous systematic reviews and meta-analyses on daridorexant and other DORAs have been published, none have specifically examined the dose-response of a DORA [29,30].

The benefit of this analysis is that pooling the individual or aggregated data from the separate studies provides a more precise estimate of

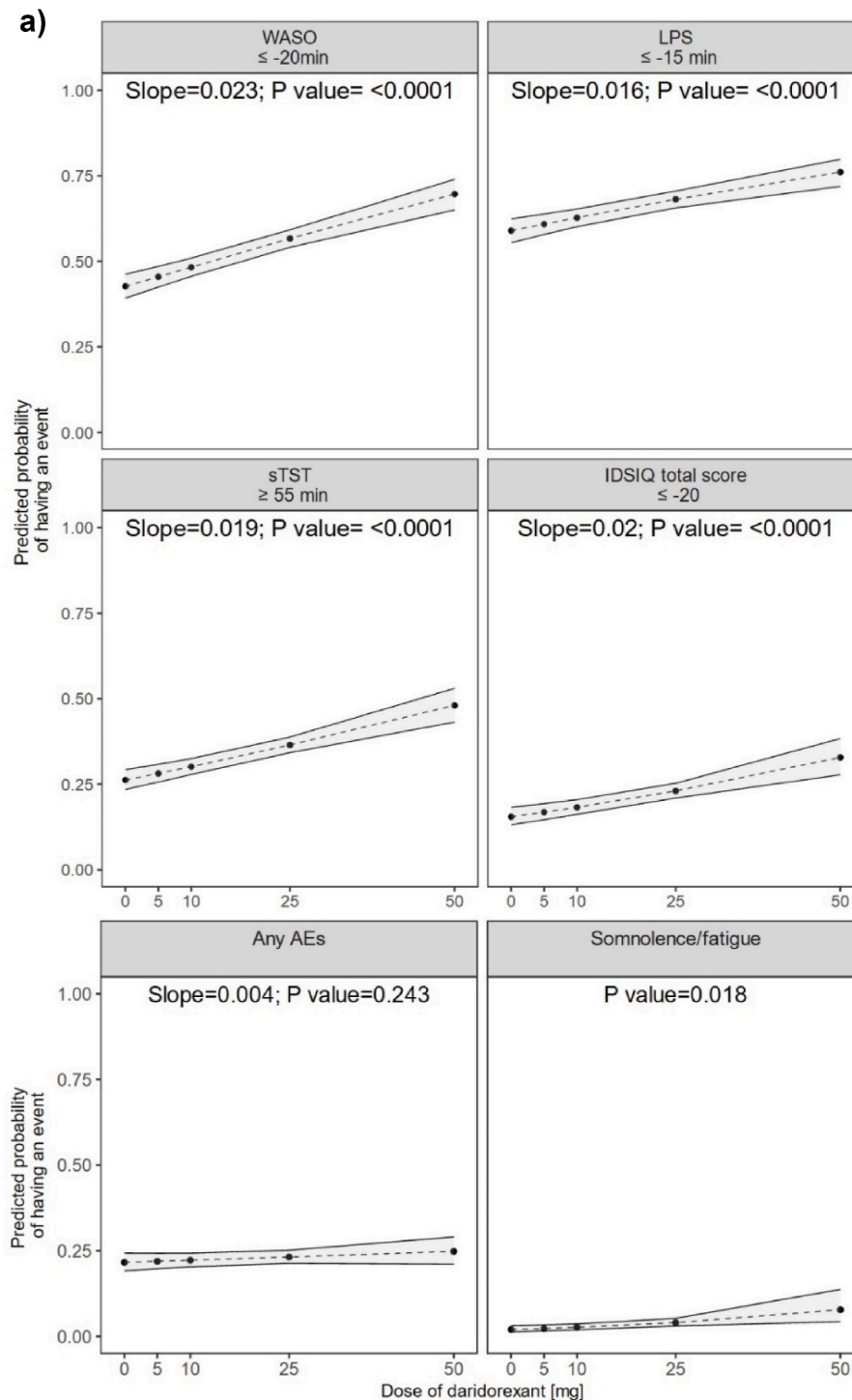


Fig. 3. Model probabilities of being a responder or having at least one adverse event at Month 1
a) Model probability based on IPD logistic regression with fixed effect approach at Month 1. Predicted probability [95 % confidence limit] and estimate and p value for the dose-response (slope); b) Two-stage meta-analysis on aggregate data based on two-stage model with random-effect approach, the solid and dashed lines correspond to the estimation of the risk ratio (with placebo as reference) and associated 95 % confidence limit. The p values assess the evidence of a dose-response. The circle represents the observed value for each dose by individual study; size of the circle is proportional to the precision (inverse of variance) of the risk ratio. AE, adverse event; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; IPD, individual patient data; LPS, latency to persistent sleep; sTST, self-reported total sleep time; WASO wake time after sleep onset.

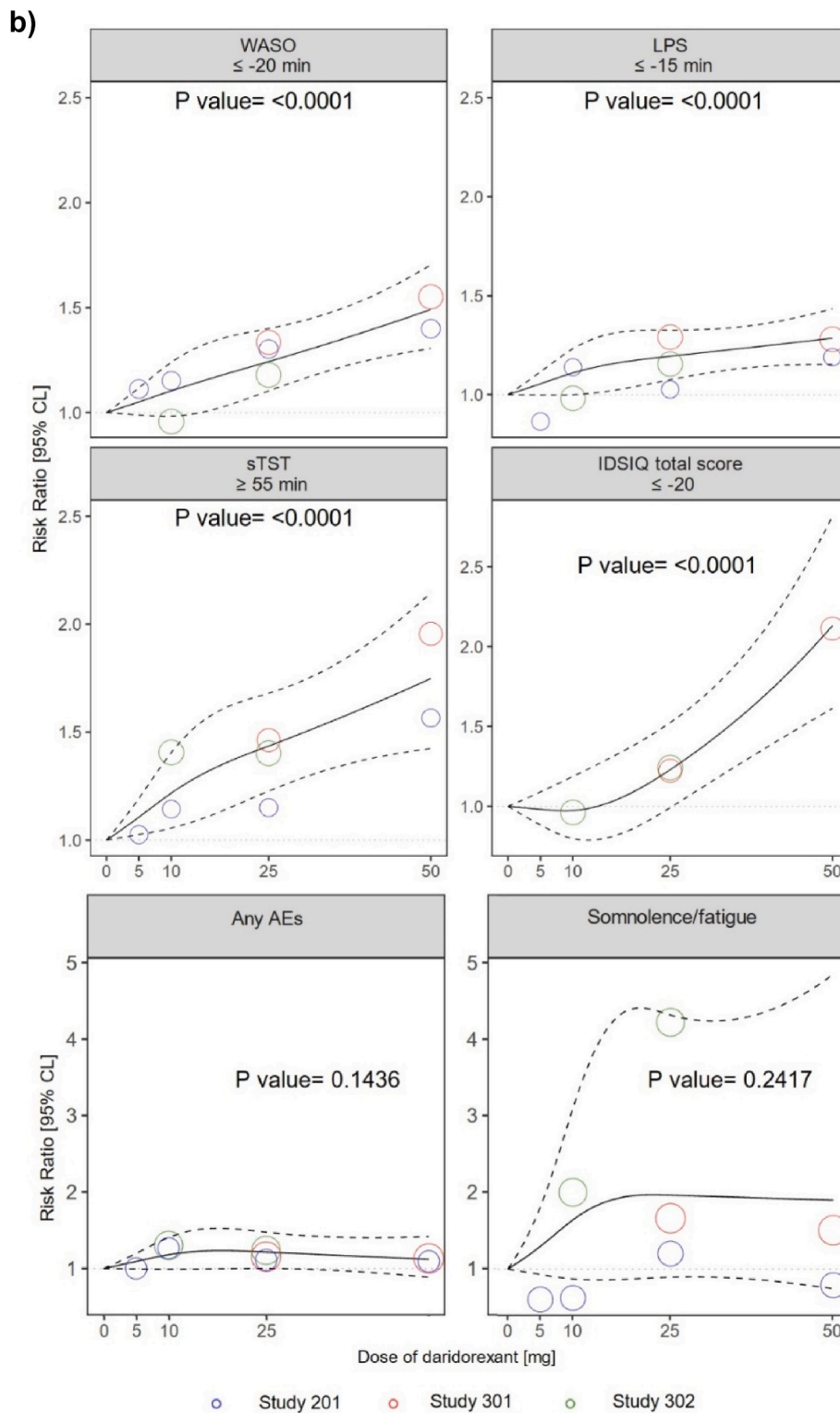


Fig. 3. (continued).

the dose-response relationship. In this post-hoc analysis, two methods were used, with the two-stage meta-analysis approach requiring no assumptions on the shape of the dose-response. The present work removes uncertainty that can arise from a single study; for example, in the 201 study, a clear linear dose-response was seen for WASO between 5 mg and 50 mg, while the dose-response between 10 mg and 50 mg was less clear for LPS [15]. This analysis also removes the uncertainty from inconsistent results across studies on a given endpoint; for example, results from

studies 301 and 302 [16] did not provide independent replication of the efficacy of daridorexant on the IDSIQ endpoint and as a consequence, the FDA considered that the strength of the evidence on daytime symptoms (as measured by the IDSIQ) was insufficient for labeling purposes. Substantial evidence of efficacy as a basis for registration is generally understood as requiring at least two adequate, well-controlled studies [31]. This approach is intended to minimize bias and to increase confidence in treatment effect demonstrated. In this analysis, the

Table 3

Prevalence of treatment-emergent adverse events: all AEs and AEs denoting somnolence/fatigue in each study at Month 1.

Prevalence n/N (%)	Daridorexant dose				
	0 mg	5 mg	10 mg	25 mg	50 mg
All adverse events					
201	18/60 (30)	18/60 (30)	22/58 (37.9)	20/60 (33.3)	20/61 (32.8)
301	63/309 (20.4)	na	na	73/310 (23.5)	71/308 (23.0)
302	53/306 (17.3)	na	69/306 (22.5)	66/308 (21.4)	na
Somnolence/fatigue					
201	5/60 (8.3)	3/60 (5.0)	3/58 (5.2)	6/60 (10.0)	4/61 (6.5)
301	6/309 (1.9)	na	na	10/310 (3.2)	9/308 (2.9)
302	4/306 (1.3)	na	8/306 (2.6)	17/308 (5.5)	na

na, not applicable.

evidence of a dose-response on daytime functioning assessed by the IDSIQ makes chance as a reason for the effect highly unlikely.

Interestingly, a non-linear dose-response shape was observed for LPS. In the Phase 3 clinical trials, the mean improvement in LPS (i.e. sleep onset) at Month 1 was approximately similar (~30 min) for daridorexant 25 and 50 mg [16]. As sleep onset is induced in the first part of the night, it could be speculated that the plasma concentrations at a dose of 25 mg, which peak within 60 min of drug intake, are sufficiently high to elicit a similar reduction in LPS as a higher dose of 50 mg [13]. In contrast, the linear dose-response seen for WASO (i.e., sleep maintenance), whereby a better effect is demonstrated for the highest dose (50 mg), could be explained by the attainment of higher plasma concentrations with 50 mg throughout the entire night.

Establishing efficacy at a higher dose should always be weighed against the risk of side effects. Dose-response relationship with AEs was thus characterized with focus on AEs denoting somnolence and fatigue, given that they are the most common adverse reactions across drugs labeled for the treatment of insomnia [30]. No dose-response relationship was observed within the dose range studied for AEs, including those denoting somnolence/fatigue. The results of the IPD analysis might suggest an increase in the incidence of somnolence/fatigue from 25 mg to 50 mg. This was however due to study 302 which did not include the highest dose of 50 mg, and the IPD analysis assumed a linear dose-response in the dose range up to 50 mg. Indeed, the analysis of aggregated data that does not make any assumption on the shape of the dose-response showed no evidence of dose dependency for safety endpoints, and rather a plateau between daridorexant 25 mg and 50 mg. This further highlights the importance of combining studies and using different analysis models. This is why the Multiple Comparison Procedure-Modelling (MCP-Mod) hybrid approach is commonly used in dose-finding studies, as it bases the analysis on a set of candidate dose-response shapes: e.g., linear, E_{max} , exponential, to best cover the dose-response relationship [32,33]. Overall, our dose-response analyses show that while daridorexant 25 mg and 50 mg are both effective doses compared with placebo, starting on 50 mg can provide the greatest benefit with regards to both night and day efficacy parameters and is not associated with any increased risk in side effects. This is contrary to the common general practice that for insomnia drugs, especially for treating chronic insomnia, the lowest effective dose should be used in order to minimize side effects, and if necessary, depending on clinical response and tolerability, to titrate to higher recommended doses [6,34]. The present results are supported by those from a recently published network meta-analysis of results for daridorexant that showed that daridorexant 50 mg was the most effective dose compared to 10 mg and 25 mg [29].

Key strengths of this analysis include the methodological quality of the three global studies on which the analyses are based, as well as the number of patients pooled, and the multiple endpoints evaluated. Study design, endpoint collection instruments and patient populations were similar across the studies and tests for heterogeneity on the treatment effect showed no evidence of heterogeneity. BMI and age were slightly different between the considered studies, however we would not expect

these to influence the results; pharmacokinetic modeling of daridorexant has indicated that differences in plasma concentration of the drug between subjects with different BMI and age are negligible [35]. In addition, clinical data have confirmed that the efficacy and safety of daridorexant in patients with insomnia disorder are comparable between older and younger adults [36]. A further strength of our analyses derives from the use of two different statistical modeling approaches, a linear model based on the totality of individual patient data and a two-stage meta-analysis approach based on summarized individual patient data without assumption on the dose-response shape. Other differences on how the two approaches were applied in this analysis include the adjustment for patient characteristics (IPD model adjusted for baseline value and age at screening if applicable; two-stage analysis – no adjustments) and the choice of fixed (IPD approach) or random (two-stage analysis) effects. Results were generally consistent using both approaches, thus supporting the robustness of the results.

Despite its strengths, our analyses have limitations that should be acknowledged. The analyses included only three studies and as the Phase 2 study had a 30-day treatment period, the main analyses are based on pooled data at Month 1, a relatively short period of treatment, during which all efficacy or safety responses may not be evident. We did however repeat the analyses at Month 3 using data from the two Phase 3 studies and the dose-response relationships were consistent to what was observed at Month 1. Given the stringent eligibility criteria and limited ethnic and racial diversity across the studies, this population may not be fully representative of the diversity of patients with insomnia disorder in the real-world. In addition, the patient population is limited to those with more moderate to severe insomnia ($ISI \geq 15$) which may not be reflective of the broader insomnia population. The results do not provide information about doses above 50 mg, which is the maximum dose of daridorexant studied in insomnia clinical trials in which the plateau of efficacy does not seem to have been reached. It should also be acknowledged that these analyses are not applicable to special populations of patients, such as those with moderate hepatic impairment or taking moderate CYP3A4 inhibitors, where 25 mg is recommended as the maximum daily dose.

3.4.1. Conclusion

Selecting the appropriate dose is critical during drug development, as well as in the clinical setting, and both efficacy and safety must be taken into account. The data presented here support the use of 50 mg as the preferred dose for daridorexant in patients with insomnia disorder to provide the greatest opportunity for efficacy with no increased risk for AEs, including somnolence/fatigue, as compared to lower doses. This information should help clinicians and their patients in decision making for optimal drug dosing and patient care.

Data availability

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.

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Ethical approval

The protocols of the three studies included in this analysis were approved by the appropriate institutional review boards or independent ethics committees and the studies were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

This is a retrospective study and formal consent is not required for this type of study.

Authorship contribution statement

PPL, GB, AO and JL were involved in the conception and design of the analysis, and all authors were involved in the interpretation of the data and in the drafting of the first version of the manuscript. PPL and JL were also involved in the acquisition and formal analysis of the data and creation of 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.

CRediT authorship contribution statement

Pierre-Philippe Luyet: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **William V. McCall:** Writing – review & editing, Writing – original draft, Investigation. **Claudio L.A. Bassetti:** Writing – review & editing, Writing – original draft, Investigation. **Guy Braunstein:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Johann Laurent:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antonio Olivieri:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Jan Hedner:** Writing – review & editing, Writing – original draft, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

All authors report article publishing charges, statistical analysis, and writing assistance were provided by Idorsia Pharmaceuticals Ltd. Antonio Olivieri reports a relationship with Idorsia Pharmaceuticals Ltd that includes: employment and equity or stocks. Guy Braunstein reports a relationship with Idorsia Pharmaceuticals Ltd that includes: employment and equity or stocks. Pierre-Philippe Luyet reports a relationship with Idorsia Pharmaceuticals Ltd that includes: employment. Johann Laurent reports a relationship with Idorsia Pharmaceuticals Ltd that includes: employment. William V McCall reports a relationship with Idorsia Pharmaceuticals Ltd that includes: consulting or advisory.

William V McCall reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. William V McCall reports a relationship with Carelon that includes: consulting or advisory. Claudio Bassetti reports a relationship with Bioproject that includes: consulting or advisory. Claudio Bassetti reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory. Claudio Bassetti reports a relationship with Jazz Pharmaceuticals Inc that includes: consulting or advisory. Claudio Bassetti reports a relationship with Idorsia Pharmaceuticals Ltd that includes: consulting or advisory. Jan Hedner reports a relationship with Somnomed that includes: funding grants. Jan Hedner reports a relationship with Desitin GmbH that includes: funding grants.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2024.07.019>.

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