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Impact of lemborexant treatment on insomnia severity: analyses from a 12-month study of adults with insomnia disorder

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Original Article

Impact of lemborexant treatment on insomnia severity: analyses from a 12-month study of adults with insomnia disorder

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ABSTRACT

Objective/background: Evaluate changes in insomnia severity in subjects with moderate to severe insomnia (Insomnia Severity Index [ISI] score ≥15) treated for 12 months nightly with lemborexant.
Patients/methods: This phase 3 randomized study comprised two 6-month treatment periods. In Period 1, 949 subjects were randomized to placebo, lemborexant 5 mg (LEM5) or 10 mg (LEM10). In Period 2, placebo subjects were rerandomized to LEM5 or LEM10; subjects initially randomized to *lemborexant* continued their assigned treatment. Insomnia severity was assessed using baseline ISI and 1-, 3-, 6-, 9-, and 12-month post-treatment scores.
Results: Mean ISI scores improved significantly across treatment groups and disease severities, with greater decreases from baseline in the LEM5 and LEM10 versus placebo groups at months 1 (−7.1, −7.2, −5.2, respectively), 3 (−8.6, −8.9, −6.1, respectively), and 6 (−9.9, −9.8, −7.2 respectively); ISI score improvements were maintained with LEM5 and LEM10 at months 9 (−11.1 and −11.2, respectively) and 12 (−11.5 and −11.2, respectively). At months 1, 3, and 6, significantly more treatment responders (≥7-point ISI score decrease from baseline) were observed with LEM5 (44%–57%) and LEM10 (44%–52%) versus placebo (30%–41%). At months 1, 3, and 6, more remitters (ISI total score <10 and < 8) were observed with LEM5 (30%–44% and 22%–34%, respectively) and LEM10 (31%–41% and 22%–31%, respectively) versus placebo (18%–28% and 11%–21%, respectively).
Conclusions: Lemborexant significantly reduced insomnia severity for 12 months and increased clinically meaningful response and remission rates versus placebo.
Clinical trial registration: ClinicalTrials.gov, NCT02952820; ClinicalTrialsRegister.eu, EudraCT Number 2015-001463-39.

1. Introduction

Insomnia, a disorder characterized by difficulties in falling asleep and/or staying asleep, and impaired daytime function or distress is the most common sleep-wake disorder [1]. While insomnia has been shown to negatively impact overall health and increase health care utilization [2–4], severity of insomnia (ie, the severity of both nighttime symptoms and associated daytime functional impairments) has also been shown to be an important health determinant. In studies over the past 10 years, more severe insomnia has been associated with diminished well-being and quality of life; increased anxiety, depression, and suicidal ideation; increased use of alcohol; reduced likelihood of remission from major depressive disorder; greater use of health care resources; increased health care costs; and increased physical symptoms

Abbreviations: DORA, dual orexin receptor antagonist; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition; FAS, Full Analysis Set; ISI, Insomnia Severity Index; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg.

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including pain and fatigue [5–13]. Studies also showed that reductions in insomnia severity were associated with reductions in the severity of comorbid conditions, such as depression [14]. Together, these studies suggest that improvements in insomnia disorder severity are an important consideration in the care of patients with insomnia.

Current treatment options for insomnia include cognitive behavioral therapy, sedative-hypnotic benzodiazepines and non-benzodiazepines, melatonin receptor agonists, sedating antidepressants, sedating antihistamines, and dual orexin receptor antagonists (DORAs) [15]. Sleep-promoting therapies have typically been assessed based on their effect on nocturnal symptom endpoints (ie, total sleep time, sleep latency, and wake after sleep onset as measured by polysomnography and patient reports) [15].

Insomnia is characterized by physiological and cognitive hyperarousal, both of which likely contribute to the inability to initiate and/or maintain sleep [16]. The orexin neuropeptide signaling system is involved in the regulation of arousal and wakefulness [17]. Thus, orexin receptor antagonism may serve as a therapeutic mechanism to manage sleep disturbances specifically and insomnia disorder severity overall. However, no studies have been published to date that examine the long-term benefit of orexin receptor antagonists at therapeutic dosages on insomnia severity, as assessed by the Insomnia Severity Index (ISI), for up to 12 months.

Lemborexant is a DORA approved in multiple countries, including the United States, Japan, Canada, Australia, and several Asian countries for the treatment of adults with insomnia. Lemborexant is a competitive antagonist at orexin receptor types 1 and 2 [18]; therefore, as a DORA, lemborexant reduces wakefulness by attenuating orexin-mediated wake drive. The efficacy and safety of lemborexant in insomnia disorder were examined in two pivotal phase 3 clinical studies. In these studies, patient-reported (sleep diary) sleep measures, including larger and statistically significant decreases in sleep onset latency and wake after sleep onset, were observed over 6 months comparing lemborexant with placebo [19]. The benefits of lemborexant were maintained across 12 months of nightly treatment [20]. A second phase 3 study, E2006-G000-304 (SUNRISE-1; NCT02783729), demonstrated significant benefit of lemborexant on polysomnographic measures of sleep onset and maintenance compared with placebo and zolpidem tartrate extended release over 1 month [21]. Lemborexant was well tolerated in both studies, with the majority of treatment-emergent adverse events as mild or moderate in severity [19–21]. These endpoints typically reflect the outcome on a particular endpoint (ie, nocturnal insomnia symptoms), which are more an index of improvement in nocturnal sleep than insomnia disorder severity. Importantly, insomnia disorder is more than a nocturnal disorder—it is associated with concurrent daytime impairments [22].

As a diagnosis of insomnia disorder is symptom-based, patient-reported outcomes provide a valid measure of treatment efficacy. The severity of insomnia is routinely assessed using the self-report ISI questionnaire [23]. The ISI is a reliable and validated instrument [24] that assesses the severity of insomnia based on patients' symptoms and their associated impact on sleep patterns, interpersonal factors, daily functioning, and worry or distress, factors that are all considered in the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (*DSM-5*) [22] diagnostic criteria of chronic insomnia. Previous research has utilized the ISI to assess improvement in insomnia severity after treatment with sleep-promoting agents. For example, greater improvements on the ISI have been observed with doxepin [25] and eszopiclone [26,27] compared with placebo over 3 months and 6 months, respectively. In addition, several analyses demonstrated improvement in mean ISI total scores with the DORA suvorexant versus placebo [28–33], although at the approved doses of suvorexant, ISI results are only available from 1-month or 3-month measurements [29–32]. The ISI can also be used to define treatment responders and remitters [24]. Treatment response may be determined using empirically validated ISI criteria for the minimally important difference in symptomatology, whereas remission can be operationalized as a reduction in symptoms to subclinical levels [24,34].

Certainly, many studies demonstrate absolute post-treatment differences in ISI scores as a measure of treatment efficacy; however, few studies evaluate responder and remission rates in patients with insomnia. Perhaps most responder and remitter analyses have been done in benzodiazepine-treated patients with insomnia. In these studies, modest improvements are generally reported relative to placebo. For example, one study evaluating nightly treatment of primary insomnia for 6 months found that in addition to improving subjective sleep measures, eszopiclone significantly reduced insomnia severity to below clinically meaningful levels (ISI $\leq$14) in 50% of patients (vs 19% with placebo) [27]. In a similar study, patients with primary insomnia demonstrated that in addition to improving various subjective sleep measures (eg, total sleep time, wake after sleep onset), 3 months of treatment with indiplon resulted in significantly more patients meeting the responder criteria (Investigator Global Rating of Change score $\leq$2; ~55% vs 30%) and ISI remission criteria (ISI <11) compared with placebo (53%–55% vs 40%) [35]. More recently, a study to measure the effectiveness of benzodiazepine receptor antagonists in the treatment of insomnia found that although 76.7% responded to treatment (ISI score change $\geq$6 points), only 47.7% achieved remission (ISI <11) [36]. Similar analyses have been reported with the DORA, suvorexant. A pooled analysis of two phase 3 studies found higher responder (ISI $\geq$6-point improvement) rates with suvorexant compared with placebo at 1 (33.9% vs 22.9%) and 3 months (55.5% vs 42.2%) post-treatment; remitter analyses were not reported [31].

This paper presents prespecified and post-hoc analyses from subjects in Study 303 (E2006-G000-303; SUNRISE-2; NCT02952820) who reported moderate to severe insomnia at baseline (ISI total score $\geq$15). The analyses explore the question of whether nightly dosing of lemborexant for up to 1 year improves insomnia severity. This is the first long-term study of a DORA at approved therapeutic dosages on insomnia severity.

2. Methods

2.1. Study design

This report is based on prespecified and post-hoc analyses of data from Study 303. Complete study details including enrollment criteria, primary endpoints, and key secondary endpoints have been reported previously [19]. Briefly, Study 303 was a 12-month, randomized, double-blind, placebo-controlled (first 6 months [Treatment Period 1]), active-only (last 6 months [Treatment Period 2]) parallel-group study.

Study drug was administered following an approximate 2-week single-blind placebo run-in. The lemborexant doses were 5 mg (LEM5) and 10 mg (LEM10). Subjects who received placebo during Treatment Period 1 were rerandomized approximately 1:1 to LEM5 or LEM10 during Treatment Period 2; these subjects were not included in the analyses. Efficacy and safety outcomes for subjects rerandomized from placebo to lemborexant for Treatment Period 2 will be reported separately.

The study was approved by an independent Institutional Review Board and conducted in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulations.

Before any screening procedures, all study subjects provided written informed consent.

2.2. Participants

The subjects in the current study include all those in the Full Analysis Set (FAS) from Study 303. Full details of study inclusion and exclusion criteria have been reported [19]. All subjects met the *DSM-5* criteria for insomnia disorder [22]. The study included males and females ≥18 years of age with a complaint of sleep onset and/or sleep maintenance difficulties and ISI total score ≥15 [19]. Subjective sleep parameters for each treatment group were confirmed by sleep history, questionnaires and sleep diary, as previously reported [19].

2.3. ISI

The ISI was administered at baseline and at the end of months 1, 3, 6, 9, and 12. The dimensions evaluated by each of the ISI items are: (1) severity of sleep onset difficulties; (2) sleep maintenance difficulties; (3) early morning awakening problems; (4) sleep dissatisfaction; (5) interference of sleep difficulties with daytime functioning; (6) noticeability of the sleep problems by others; and (7) distress caused by sleep difficulties [23].

Each item in the ISI is scored on a five-point Likert scale ranging from 0 (no problem) to 4 (very severe problem). The ISI total score was calculated as the sum of participant responses to items 1–7. A score of 22–28 corresponds with severe insomnia, 15–21 with moderate insomnia, 8–14 with subthreshold insomnia, and 0–7 with no clinically significant insomnia [23,24].

Based on change from baseline in ISI total scores, post-hoc responder and remitter analyses were also conducted. For the responder analysis, the percentage of subjects with a decrease from baseline of ≥7 points in ISI total score after 1, 3, 6, 9, or 12 months of treatment was calculated. The rationale for this responder criterion was the finding that a decrease in ISI total score >7 identified patients with moderate improvements on the ISI in a sample population [24]. Additionally, the percentage of subjects who achieved remission from insomnia based on ISI total score <10 [24] or <8 after 1, 3, 6, 9, or 12 months of treatment was calculated. In a sample population, a cutoff score of 10 was found to be an appropriate threshold for detecting insomnia [24]. An ISI total score of <8 aligns with the disease severity category of no clinically significant insomnia (ISI total score 0–7).

2.4. Statistical analyses

ISI endpoints were assessed in the Full Analysis Set (FAS) from Study 303, defined as the group of randomized subjects who received at least one dose of study drug and had at least one postdose ISI measurement [19]. Additional analyses, where indicated, were conducted in the subgroups of subjects from the FAS with moderate insomnia at baseline (ISI total score 15–21) or severe insomnia at baseline (ISI total score 22–28).

Prespecified changes from baseline in ISI total score at the end of months 1, 3, and 6 were analyzed using a mixed-effect model repeated measurement analysis with factors for age group, region, visit (time point), treatment, and treatment-by-visit interaction as fixed effects, and the baseline ISI total score value as a covariate. Changes from baseline in ISI total score at the end of months 9 and 12 were summarized descriptively. Missing values were not imputed.

For the responder and remitter analyses, study dropouts and participants with missing information were considered nonresponders. At months 1, 3, and 6, two-sided 95% confidence intervals were calculated based on normal approximation, and *P* values for between-group comparisons were based on the Cochran–Mantel–Haenszel test stratified by region and age group.

In addition, the number and percentage of subjects in each insomnia severity category (based on ISI total score) was calculated at months 1, 3, 6, 9, and 12 in the FAS and in the subgroups of subjects in the FAS who had moderate or severe insomnia at baseline. These analyses were conducted to determine the frequency with which subjects shifted from moderate or severe insomnia at baseline to other severity categories at each time point.

3. Results

3.1. Baseline characteristics

The FAS comprised 949 subjects (placebo, n = 318; LEM5, n = 316; LEM10, n = 315). Six hundred and ninety-two subjects had moderate insomnia (ISI total score 15–21) at baseline, and 223 subjects had severe insomnia (ISI total score 22–28) at baseline. An additional 34 subjects were included in the study despite not meeting ISI inclusion criteria at baseline, as they had met the ISI ≥15 inclusion criterion at screening. One additional subject (N = 950) was added to some of the post-hoc analyses after final data reconciliation at the end of the 12-month study, as that subject's updated data met FAS criteria.

Across all severity and treatment groups, most subjects were white and female (Table 1). Across treatment arms in the FAS, mean ISI total score at baseline was approximately 19, indicative of moderate insomnia [23]. Mean ISI total score was similar across treatment groups within each insomnia severity category (Table 1).

3.2. Change from baseline in ISI total score

Mean ISI total scores decreased from baseline across all treatment groups (Fig. 1). Decreases were significantly greater with LEM5 and LEM10 compared with placebo at the end of month 1 (both comparisons, $P < 0.01$), month 3 (both comparisons, $P < 0.0001$), and month 6 (both comparisons, $P < 0.0001$; Fig. 1 and Supplementary Table 1). The decreases in ISI total score with LEM5 and LEM10 were maintained after 9 and 12 months of treatment.

3.3. Responder and remitter analyses

Significantly higher percentages of subjects achieved a decrease from baseline in ISI total score of ≥7 points (ie, were treatment responders) with LEM5 and LEM10 compared with placebo at month 1 (LEM5 = 44.0%; LEM10 = 44.4%; placebo = 29.5%; both comparisons, $P < 0.001$), month 3 (LEM 5 = 53.5%; LEM10 = 52.1%; placebo = 36.4%; both comparisons, $P < 0.0001$), and month 6 (LEM5 = 56.6%; LEM10 = 51.4%; placebo = 41.4%; $P = 0.0002$ and $P = 0.0107$, respectively; Table 2). The percentage of treatment responders was maintained at over 50% for both doses of LEM through months 9 (LEM5 = 57.3%; LEM10 = 51.1%) and 12 (LEM5 = 53.8%; LEM10 = 51.7%).

In addition to the responder analysis, two analyses were performed to identify subjects who achieved remission from insomnia, defined as reaching ISI total score <10 or <8. Significantly higher percentages of subjects with an ISI total score <10 were observed with LEM5 and LEM10 treatment compared with placebo at month 1 (LEM5 = 30.4%; LEM10 = 31.1%; placebo = 17.6%), month 3 (LEM5 = 38.0%; LEM10 = 39.4%; placebo = 24.8%), and month 6 (LEM5 = 44.0%; LEM10 = 40.6%; placebo = 27.9%) ($P < 0.001$ for all comparisons; Table 2). Among subjects treated with either dose of lemborexant, over 40% maintained remission at the level of ISI total

Table 1
Baseline demographics and characteristics.

	Full Analysis Set (N = 949)			Subjects with moderate insomnia[a] at baseline (n = 692)			Subjects with severe insomnia[b] at baseline (n = 223)		
	PBO (n = 318)	LEM5 (n = 316)	LEM10 (n = 315)	PBO (n = 241)	LEM5 (n = 222)	LEM10 (n = 229)	PBO (n = 65)	LEM5 (n = 84)	LEM10 (n = 74)
Age, y									
Mean (SD)	54.5 (14.0)	54.2 (13.7)	54.8 (13.7)	54.6 (13.9)	54.8 (13.7)	54.8 (14.1)	53.9 (14.9)	52.7 (13.8)	55.1 (12.5)
Median (range)	56 (18–83)	55 (20–85)	55 (18–88)	56 (18–83)	56 (20–85)	56 (18–88)	55 (25–83)	54.5 (20–76)	54 (24–83)
Sex, n (%)									
Male	102 (32.1)	107 (33.9)	93 (29.5)	78 (32.4)	77 (34.7)	73 (31.9)	22 (33.8)	27 (32.1)	16 (21.6)
Female	216 (67.9)	209 (66.1)	222 (70.5)	163 (67.6)	145 (65.3)	156 (68.1)	43 (66.2)	57 (67.9)	58 (78.4)
Race, n (%)									
White	232 (73.0)	222 (70.3)	225 (71.4)	166 (68.9)	154 (69.4)	165 (72.1)	57 (87.7)	61 (72.6)	54 (73.0)
Black or African American	23 (7.2)	27 (8.5)	26 (8.3)	19 (7.9)	13 (5.9)	17 (7.4)	2 (3.1)	13 (15.5)	6 (8.1)
Asian	59 (18.6)	61 (19.3)	58 (18.4)	54 (22.4)	53 (23.9)	45 (19.7)	4 (6.2)	6 (7.1)	10 (13.5)
Other	4 (1.3)	6 (1.9)	6 (1.9)	2 (0.8)	2 (0.9)	2 (0.9)	2 (3.1)	4 (4.8)	4 (5.4)
BMI, mean (SD), kg/m^2	27.2 (5.5)	27.3 (6.3)	27.2 (5.6)	27.2 (5.7)	26.9 (5.9)	27.2 (5.9)	27.4 (5.3)	28.5 (7.3)	26.9 (4.4)
ISI total score, mean (SD)	19.0 (3.1)	19.6 (3.3)	19.1 (3.4)	18.2 (2.0)	18.3 (1.9)	17.9 (1.9)	23.3 (1.3)	23.8 (1.9)	23.8 (1.6)
Sleep parameters									
sSOL, median (1st and 3rd quartiles), min	55.9 (34.1, 78.9)	53.6 (32.9, 75.7)	55.7 (33.6, 85.1)	50.0 (32.1, 72.1)	50.4 (32.9, 71.4)	52.5 (32.5, 75.8)	71.6 (46.4, 107.1)	68.6 (45.0, 94.3)	73.6 (38.6, 105.2)
sSE, mean (SD), %	61.3 (17.8)	63.1 (18.2)	62.0 (17.2)	63.7 (16.7)	65.6 (16.0)	63.3 (16.4)	51.2 (18.5)	54.0 (21.4)	56.3 (19.6)
sWASO, mean (SD),	132.5 (80.2)	132.8 (82.5)	136.8 (87.4)	123.3 (74.7)	122.4 (73.4)	128.2 (75.6)	168.9 (91.3)	168.5 (96.9)	172.8 (113.3)
sTST, mean (SD), min	304.3 (91.5)	315.5 (93.5)	306.9 (88.0)	315.3 (86.7)	328.4 (83.8)	311.0 (83.1)	257.7 (95.8)	269.1 (106.4)	283.1 (101.7)

BMI = body mass index; ISI = Insomnia Severity Index; LEM5 = lemborexant 5 mg; LEM10 = lemborexant 10 mg; PBO = placebo; SD = standard deviation; sSE = subjective sleep efficiency; sSOL = subjective sleep onset latency; sTST = subjective total sleep time; sWASO = subjective wake after sleep onset.
[a] Moderate insomnia, ISI total score 15–21.
[b] Severe insomnia, ISI total score 22–28. Of all subjects in the Full Analysis Set, 34 subjects did not meet ISI inclusion criteria at baseline (ISI total score 8–14, n = 32; ISI total score 0–7, n = 2), although they met ISI inclusion criteria at screening.

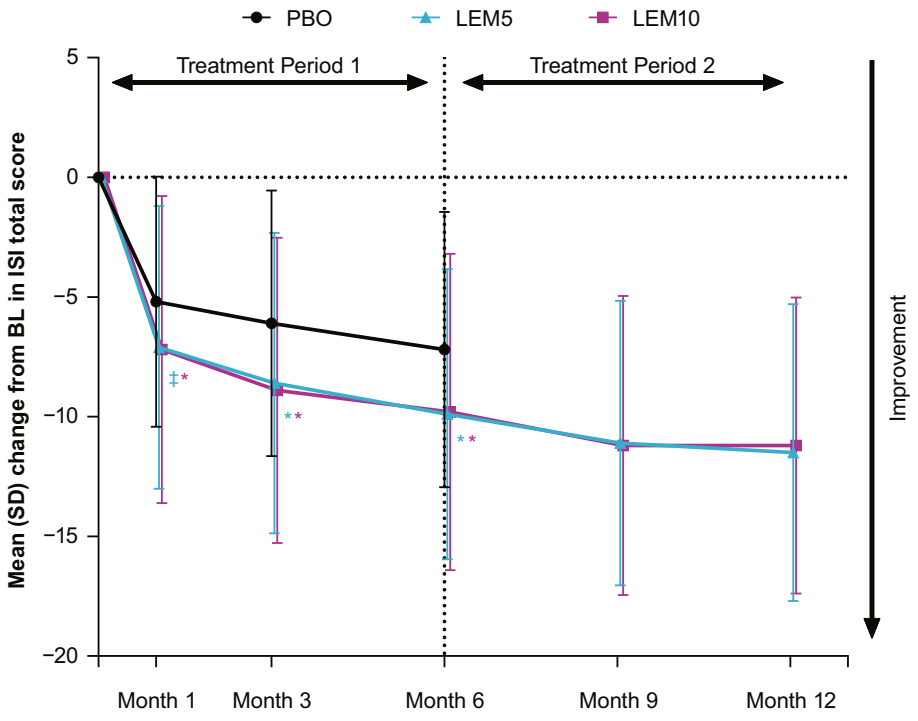

Fig. 1. Change from baseline in ISI total score across 12 months of treatment (Full Analysis Set, N = 949). *$P < 0.0001$, ‡$P < 0.01$ vs PBO. Baseline: PBO, n = 318; LEM5, n = 316; LEM10, n = 315. Month 1: PBO, n = 296; LEM5, n = 300; LEM10, n = 286. Month 3: PBO, n = 283; LEM5, n = 274; LEM10, n = 259. Month 6: PBO, n = 257; LEM5, n = 258; LEM10, n = 234. Month 9: LEM5, n = 233; LEM10, n = 205. Month 12: LEM5, n = 220; LEM10, n = 201. For months 1–6, *P* values are based on mixed-effect model repeated measurement analysis with factors for age group, region, visit (time point), treatment, and treatment-by-visit interaction as fixed effects, and baseline ISI total score value as a covariate. BL = baseline; ISI = Insomnia Severity Index; LEM5 = lemborexant 5 mg; LEM10 = lemborexant 10 mg; PBO = placebo; SD = standard deviation.

Table 2
Statistical analysis of responder and remitter rates at each study timepoint (Full Analysis Set, N = 950[a]).

	PBO (n = 319)	LEM5 (n = 316)	LEM10 (n = 315)	PBO (n = 319)	LEM5 (n = 316)	LEM10 (n = 315)	PBO (n = 319)	LEM5 (n = 316)	LEM10 (n = 315)
	Responders: ≥7-point decrease in ISI total score from baseline			Remitters: ISI total score <10			Remitters: ISI total score <8		
Month 1									
Yes, n (%)	94 (29.5)	139 (44.0)	140 (44.4)	56 (17.6)	96 (30.4)	98 (31.1)	36 (11.3)	69 (21.8)	70 (22.2)
No, n (%)	202 (63.3)	162 (51.3)	147 (46.7)	240 (75.2)	205 (64.9)	189 (60.0)	260 (81.5)	232 (73.4)	217 (68.9)
Missing, n (%)[b]	23 (7.2)	15 (4.7)	28 (8.9)	23 (7.2)	15 (4.7)	28 (8.9)	23 (7.2)	15 (4.7)	28 (8.9)
Difference of proportion vs PBO (95% CI)[c]		14.2 (6.7–21.6)	14.9 (7.5–22.3)		12.8 (6.1–19.4)	13.7 (7.1–20.3)		10.5 (4.8–16.3)	11.1 (5.3–16.8)
P value vs PBO[c,d]		0.0002	0.0001		0.0002	<0.0001		0.0004	0.0002
Month 3									
Yes, n (%)	116 (36.4)	169 (53.5)	164 (52.1)	79 (24.8)	120 (38.0)	124 (39.4)	54 (16.9)	82 (25.9)	92 (29.2)
No, n (%)	167 (52.4)	105 (33.2)	95 (30.2)	204 (63.9)	154 (48.7)	135 (42.9)	229 (71.8)	192 (60.8)	167 (53.0)
Missing, n (%)[b]	36 (11.3)	42 (13.3)	56 (17.8)	36 (11.3)	42 (13.3)	56 (17.8)	36 (11.3)	42 (13.3)	56 (17.8)
Difference of proportion vs PBO (95% CI)[c]		17.0 (9.3–24.6)	15.7 (8.1–23.4)		13.0 (5.8–20.1)	14.9 (7.7–22.1)		9.1 (2.7–15.4)	12.5 (6.1–19.0)
P value vs PBO[c,d]		<0.0001	<0.0001		0.0004	<0.0001		0.0055	0.0002
Month 6									
Yes, n (%)	132 (41.4)	179 (56.6)	162 (51.4)	89 (27.9)	139 (44.0)	128 (40.6)	66 (20.7)	106 (33.5)	99 (31.4)
No, n (%)	126 (39.5)	78 (24.7)	72 (22.9)	169 (53.0)	118 (37.3)	106 (33.7)	192 (60.2)	151 (47.8)	135 (42.9)
Missing, n (%)[b]	61 (19.1)	59 (18.7)	81 (25.7)	61 (19.1)	59 (18.7)	81 (25.7)	61 (19.1)	59 (18.7)	81 (25.7)
Difference of proportion vs PBO (95% CI)[c]		14.9 (7.2–22.5)	10.1 (2.4–17.9)		15.6 (8.3–22.9)	12.6 (5.3–20.0)		12.5 (5.6–19.3)	10.6 (3.8–17.4)
P value vs PBO[c,d]		0.0002	0.0107		<0.0001	0.0008		0.0004	0.0025
Month 9									
Yes, n (%)		181 (57.3)	161 (51.1)		143 (45.3)	140 (44.4)		111 (35.1)	111 (35.2)
No, n (%)		52 (16.5)	46 (14.6)		90 (28.5)	67 (21.3)		122 (38.6)	96 (30.5)
Missing, n (%)[b]		83 (26.3)	108 (34.3)		83 (26.3)	108 (34.3)		83 (26.3)	108 (34.3)
Month 12									
Yes, n (%)		170 (53.8)	163 (51.7)		145 (45.9)	134 (42.5)		114 (36.1)	109 (34.6)
No, n (%)		50 (15.8)	41 (13.0)		75 (23.7)	70 (22.2)		106 (33.5)	95 (30.2)
Missing, n (%)[b]		96 (30.4)	111 (35.2)		96 (30.4)	111 (35.2)		96 (30.4)	111 (35.2)

CI = confidence interval; ISI = Insomnia Severity Index; LEM5 = lemborexant 5 mg; LEM10 = lemborexant 10 mg; PBO = placebo.
[a] One patient was identified after the full database lock compared with Period 1 database lock and included in the post-hoc analysis.
[b] Study dropouts and participants with missing information were considered nonresponders.
[c] Two-sided 95% CI based on normal approximation.
[d] *P* values based on Cochran–Mantel–Haenszel test.

score <10 at months 9 (LEM5 = 45.3%; LEM10 = 44.4%) and 12 (LEM5 = 45.9%; LEM10 = 42.5%).

In the second remitter analysis, significantly more subjects receiving either LEM5 or LEM10 achieved ISI total score <8 compared with subjects receiving placebo at months 1 (LEM5 = 21.8%; LEM10 = 22.2%; placebo = 11.3%), 3 (LEM5 = 25.9%; LEM10 = 29.2%; placebo = 16.9%), and 6 (LEM5 = 33.5%; LEM10 = 31.4%; placebo = 20.7%) ($P < 0.01$ for all comparisons; Table 2). With either dose of lemborexant, more than one-third of subjects maintained this level of remission through months 9 (LEM5 = 35.1%; LEM10 = 35.2%) and 12 (LEM5 = 36.1%; LEM10 = 34.6%).

3.4. Distribution of disease severity category by timepoint and baseline severity

In the FAS, the proportions of subjects with moderate or severe insomnia decreased at each time point, and the total proportion of subjects with subthreshold or no clinically significant insomnia increased correspondingly (Fig. 2A). Among lemborexant-treated subjects with moderate insomnia at baseline (Fig. 2B), most subjects shifted to less severe insomnia categories after 1 month of treatment, and 80% or more had subthreshold or no clinically significant insomnia (ISI total score ≤14) from months 6 to 12. At month 3 and beyond, the majority of lemborexant-treated subjects with severe insomnia at baseline met criteria for subthreshold or no clinically significant insomnia (Fig. 2C).

4. Discussion

The findings from these analyses demonstrate a decreased insomnia severity with lemborexant treatment across 12 months and support the previously reported benefit of lemborexant on nighttime measures of insomnia [19,20]. The study also demonstrated that a significant number of subjects achieve a meaningful reduction in insomnia severity as early as 1-month post-treatment that lasts through at least 12 months.

The responder and remitter analyses in the current study are important ways to evaluate efficacy. As noted earlier, nearly half of lemborexant-treated patients were responders (≥7-point decrease in ISI score) as early as 1 month post-treatment, which increased to almost 60% by the 3-month evaluation and persisted at >50% up to the end of the 12-month analysis. Interestingly, we did not observe a dose-dependent relationship in responder and remitter rates with LEM5 and LEM10, nor was a dose response observed in the analysis of change from baseline in ISI total score. These findings suggest that both doses of lemborexant produce similar efficacy profiles. In Study 303, subjects were not permitted to adjust their lemborexant dose. The recommended starting dose for lemborexant is 5 mg, however, it is possible that some patients may derive additional benefit from the higher 10 mg dose, depending on response and tolerability.

Limited data showing clinically meaningful and significant reductions in insomnia severity are available for other DORAs. Of available responder analyses, treatments are generally reported for shorter than the 12-month duration shown in the current lemborexant study. At the approved doses of suvorexant, ISI results are available through 1–3 months of treatment [29–32] and demonstrate similar outcomes as reported with lemborexant. That is, a larger proportion of responders (≥6-point decrease in ISI score from baseline) [29–31] as well as a higher proportion of remitters (ISI total score <10) [30] was found for subjects treated with suvorexant at approved doses versus placebo as assessed at 3 months of treatment. A recent phase 2 study in 359 subjects of an investigational DORA, daridorexant, found that ISI scores did not show a dose-dependent relationship over the 1-month study despite sustained reductions of wake after sleep onset and latency to persistent sleep by polysomnography over the treatment period; the absolute change in ISI score from baseline to day 30 was similar between placebo and daridorexant and smaller than the zolpidem comparator despite objective polysomnography measures [37]. The small sample sizes across the daridorexant doses (5, 10, 25, 50 mg) may limit the interpretation of these findings.

The improvement in insomnia severity and long-term remission rates we observed with lemborexant may have significant implications on long-term improvements in quality of life, daytime functioning, and morbidity associated with insomnia; these variables were not evaluated in the current analysis. Limited systematic studies have evaluated the relationship between successful long-term insomnia treatment and improvement of adverse consequences; however, of those available, most show a positive relationship. Several independent 6-month studies of pharmacologic treatment for primary insomnia found that in addition to significant improvement in efficacy on sleep parameters, patient-reported daytime alertness and concentration, ability to function during the daytime, and physical sense of well-being improved [27,38–40]. Improvements have also been reported in patients with comorbid sleep disorders. One study of patients with comorbid insomnia and rheumatoid arthritis, and another with comorbid periodic limb disorder and excessive daytime sleepiness, showed lower-than-optimal daytime alertness improved significantly in addition to improved sleep [41,42]. Similarly, a 6-month study of eszopiclone for the treatment of chronic insomnia in patients with and without comorbid psychiatric disorders, including major depressive disorder and generalized anxiety disorder, demonstrated significant long-term improvements across numerous sleep parameters, as well as improvements in mental health scores in patients with psychiatric comorbidities [43]. Whether the long-term remission observed with lemborexant is associated with similar long-term improvements in conditions seen in chronic insomnia remains to be seen. Indeed, investigation into this relationship is warranted in future studies.

4.1. Study strengths and limitations

Study 303 was a large, global, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that extended through 12 months of treatment. Few other studies have examined the long-term impact of insomnia medications on insomnia severity. Additionally, the use of a well-accepted patient-reported outcome measure (ie, ISI) to document response and remission in this study adds to the evidence provided by other metrics (diary and polysomnography) in documenting the beneficial clinical impact of lemborexant treatment for insomnia; the ISI may better reflect patients' subjective complaint than other metrics typically used for measuring treatment outcome [23,24].

This study enrolled patients using *DSM-5* criteria for insomnia disorder, thus allowing for subjects with some well-managed comorbid conditions, as previously described [19,20]. Therefore, it is possible that in a subset of subjects, comorbidities may have contributed to the persistence of moderate to severe insomnia. Larger studies are needed to define predictors of "nonresponders."

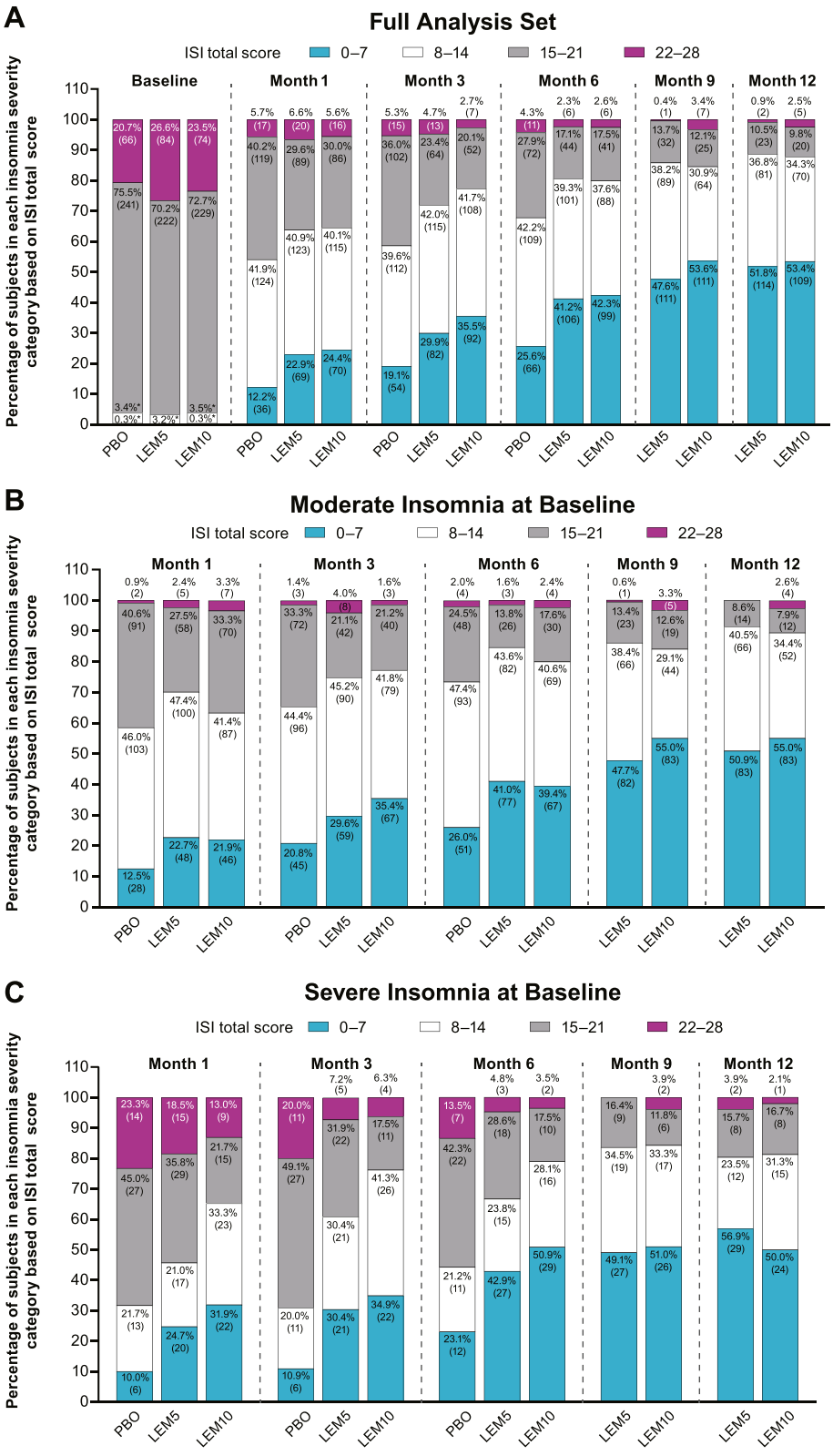

Fig. 2. Distribution of disease severity (based on ISI total score) at each study timepoint for (A) Full Analysis Set (N = 950*) (B) subjects with moderate insomnia (ISI total score 15–21) at baseline (n = 692), and (C) subjects with severe insomnia (ISI total score 22–28) at baseline (n = 224). ISI total score 0–7, no clinically significant insomnia; ISI total score 8–14, subthreshold insomnia; ISI total score 15–21, moderate insomnia; ISI total score 22–28, severe insomnia. Panels B and C represent shift from moderate or severe (respectively) baseline severity to each post-treatment severity category at each time point. *One subject was identified after the full database lock compared with the Period 1 database lock and included in the post-hoc analysis. Number in parentheses represents the total number of subjects in the corresponding insomnia severity category at the indicated time point. FAS: PBO, n = 319; LEM5, n = 316; LEM10, n = 315. Subjects with moderate insomnia at baseline: PBO, n = 241; LEM5, n = 222; LEM10, n = 229. Subjects with severe insomnia at baseline: PBO, n = 66; LEM5, n = 84; LEM10, n = 74. *Of all subjects in the FAS, 34 subjects did not meet ISI inclusion criteria at baseline (ISI total score 8–14, n = 32; ISI total score 0–7, n = 2), although they met ISI inclusion criteria at screening. FAS = Full Analysis Set; ISI = Insomnia Severity Index; LEM5 = lemborexant 5 mg; LEM10 = lemborexant 10 mg; PBO = placebo.

It should be noted that the analyses of responders and remitters, distribution of disease severity, and participant subgroups with moderate or severe insomnia were post-hoc analyses.

5. Conclusions

Overall, findings from this study suggest that the previously demonstrated benefit of lemborexant on subjective sleep measures correlate with reductions in insomnia symptom severity. Compared with placebo, LEM5 and LEM10 treatment significantly decreased the severity of insomnia symptoms, as assessed by mean ISI total score, and increased the proportions of responders and remitters. Improvements in insomnia severity were maintained over 12 months of treatment and were seen in the subgroups of subjects with either moderate or severe insomnia determined at baseline.

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Author contributions

All authors have made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of interest

TR has consulted for Eisai, Idorsia, Jazz Pharmaceuticals, Merck & Co., Orexo, SEQ, and Takeda. RR has received grant/research support from Eisai, Idorsia, Merck & Co., and Vanda Pharmaceuticals. CM has received research support from Canopy Health, Eisai, Idorsia, and Lallemand Health Solutions; he also served on advisory boards for Eisai, Merck & Co., Pear Therapeutics, Sunovion Pharmaceuticals, and Weight Watchers. JY and KP are employees of Eisai Ltd. CP, EP, MMalhotra, and MMoline are employees of Eisai Inc., NA, Jr., is a former employee of Eisai, Inc.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2022.01.024

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.01.024

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