Title

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Journal

Nihon shinkei seishin yakurigaku zasshi = Japanese journal of psychopharmacology, 45(1)

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Publication Date

2025-03-01

DOI

10.1002/npr2.12509

Peer reviewed

Received: 9 April 2024 | Revised: 13 November 2024 | Accepted: 18 November 2024

DOI: 10.1002/npr2.12509

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

ORIGINAL ARTICLE

Efficacy and safety of lemborexant in subjects with insomnia disorder receiving medications for depression or anxiety symptoms

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Funding information
Eisai Inc., Grant/Award Number: N/A

Abstract

Aim: Individuals with insomnia frequently have comorbid depression or anxiety. This study sought to provide a preliminary indication of the effects of lemborexant (LEM) in subjects treated for mild depression/anxiety symptoms.

Methods: E2006-G000-303 (NCT02952820; EudraCT 2015-001463-39; SUNRISE-2) was a 12-month, phase 3, randomized, placebo-controlled, double-blind study where subjects with insomnia disorder were randomized (1:1:1) to placebo, LEM 5 mg (LEM5), or LEM 10 mg (LEM10) for 6 months. During the second 6 months (not reported), placebo-treated subjects were re-randomized to LEM5 or LEM10. In this post hoc analysis, changes from baseline (CFB) in subject-reported (subjective) sleep onset latency (sSOL), sleep efficiency (sSE), wake after sleep onset (sWASO), total sleep time (sTST), Fatigue Severity Scale, and Insomnia Severity Index were evaluated in subjects treated with medications for symptoms of depression/anxiety (subpopulation).

Results: Of 949 randomized subjects, 61 treated with medications for symptoms of depression/anxiety were included. In the subpopulation, CFB comparing LEM with placebo were generally smaller than the overall population due to a larger placebo response in the subpopulation. However, the magnitudes of CFB within the active treatment groups for sSOL, sWASO, sTST, and sSE were similar between the subpopulation and the overall population. No new safety signals were observed in the subpopulation.

Conclusion: LEM treatment benefited subjects with insomnia treated with medications for depression/anxiety symptoms, with no new safety signals. A greater placebo response in the subpopulation than in the overall population decreased the drug versus placebo effect size for LEM, as has been reported for other insomnia medications.

Manoj Malhotra: Former employee.

KEYWORDS
antidepressant, anxiolytic, dual orexin receptor antagonist, insomnia disorder, lemborexant

1 | INTRODUCTION

Depression and anxiety symptoms are common in patients with insomnia. Insomnia and depression can have a bidirectional etiologic relationship, insomnia being a common complaint in patients with depression, while depression develops in many patients with insomnia.[1,2] Approximately 90% of patients with clinical depression suffer from sleep disturbance,[1,3] and in a study by Ohayon and Lemoine,[4] 11% of subjects with insomnia symptoms had concomitant depressive disorders. More severe insomnia symptoms correlate with greater severity of depression and reduce the likelihood that remission from major depressive disorder (MDD) will be achieved.[5,6] Insomnia is both a prodrome for depression and an independent risk factor for its emergence or recurrence,[7] and this relationship is retained even after adjusting for demographics and multiple medical conditions.[8]

The bidirectional relationship between insomnia and depression suggests that treating insomnia in patients with depression could improve both mood and sleep. A systematic review and meta-analysis published in 2018 by Gebara and colleagues[9] showed that treatment of insomnia symptoms in patients with insomnia and depression symptoms could positively impact depression, although many of the studies presented in the analysis did not achieve statistical significance. Data from a more recent randomized phase 2b trial of seltorexant, a selective orexin-2 receptor antagonist given as adjunctive therapy targeting insomnia symptoms in subjects with MDD with inadequate response to selective serotonin reuptake inhibitors (SSRI)/serotonin-norepinephrine reuptake inhibitors (SNRI), showed a clinically meaningful reduction in depressive symptoms over up to 6 weeks in subjects in the seltorexant 20 mg group; this dose was more effective in subjects with insomnia symptoms (Insomnia Severity Index [ISI] ≥15) than those without significant insomnia symptoms.[10] In addition, there was a clinically meaningful improvement in ISI scores at week 6 in the seltorexant 20 mg and 40 mg groups compared with the placebo group. Randomized clinical trials also have shown that treatment of subjects with insomnia disorder and depression disorder who are on a stable dose of an antidepressant medication with a hypnotic (zolpidem) can improve subject-reported sleep, daytime functioning, and concentration relative to placebo[11] and decrease suicidality, especially in suicidal subjects with severe baseline insomnia.[12] Other recent randomized clinical trials have shown that use of cognitive behavioral therapy (CBT) in adults with insomnia disorder with and without depression symptoms, in older adults (≥60 years of age) with insomnia disorder but not depression disorder, and in pregnant women can prevent the development of depression while improving insomnia remission rates.[13–15] Subjects who are treated for MDD frequently have residual sleep symptoms, and treatment of these symptoms with CBT favorably impacts sleep and depression scores,[16,17] suggesting that ideal symptom relief may require combination treatment for both depression and insomnia.

Plain Language Summary

People with insomnia may also have depression or anxiety and may be taking medicines for those symptoms. In the SUNRISE-2 study, adults (18 years and older) with insomnia reported improved sleep with lemborexant, which is approved to treat adults with insomnia, compared with people treated with placebo for 6 months; the sleep benefits of lemborexant were maintained through at least 1 year. This post hoc study examined whether lemborexant can improve sleep in people taking concomitant medications for depression or anxiety symptoms, using a subset of people from the SUNRISE-2 study. Of the 949 adults with insomnia in SUNRISE-2, data from 61 people taking concomitant medication for symptoms of depression or anxiety were analyzed. The results showed that in people taking concomitant medications for depression or anxiety symptoms, lemborexant helped more people to fall asleep and stay asleep compared with people taking placebo. The safety of lemborexant in this subset of people was not clinically meaningfully different from the safety in the overall population from the SUNRISE-2 study. These results provide an indication of a positive effect of lemborexant on sleep in people who are also being treated for symptoms of depression or anxiety, but more studies are needed to confirm these results.

Like depression, anxiety is common in individuals with insomnia. Insomnia/sleep disturbances affect approximately 50% of individuals with anxiety disorders.[18] Among French individuals reporting insomnia, generalized anxiety disorder (GAD) was among the most commonly diagnosed psychiatric disorder.[19] As with depression, insomnia and GAD may have a reciprocal relationship.[20]

Compared with insomnia and depression, clinical trials involving subjects with insomnia and anxiety, specifically GAD, have been relatively rare. However, data suggest that dual treatment may also be beneficial for subjects with concomitant insomnia and anxiety disorders. Although one randomized double-blind study assessing the impact of dual therapy in subjects with comorbid insomnia and GAD showed that the addition of zolpidem to escitalopram did not improve anxiety symptoms,[21] another randomized double-blind study showed that the addition of eszopiclone to escitalopram did improve anxiety[22]; in both studies sleep symptoms did improve with combination compared with monotherapy

(zolpidem extended-release/escitalopram vs. placebo/escitalopram and eszopiclone/escitalopram vs. escitalopram/placebo). More recently, in a small ($N = 24$) single-arm trial involving subjects with insomnia disorder and GAD, the use of CBT for insomnia was associated with moderate-to-large effect sizes for improvement in GAD symptoms, depression, functional impairment, and quality of life, as well as insomnia symptoms.[20]

Lemborexant (LEM) is a competitive dual orexin receptor antagonist approved in multiple countries, including the United States, Canada, Australia, Japan, and several other Asian and Middle Eastern countries, for the treatment of adults with insomnia disorder. In Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820; EudraCT 2015–001463-39), LEM 5 mg (LEM5) and LEM 10 mg (LEM10) provided significant benefits on subject-reported (subjective) sleep onset and sleep maintenance outcomes compared with placebo over 6 months,[23] with LEM benefits maintained through 12 months.[24] Study 303 was conducted after the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5)[25] criteria for insomnia disorder were updated in 2013 to include those with insomnia occurring with psychiatric conditions. This resulted in the inclusion of study subjects treated with antidepressants and with comorbid mild depression or anxiety symptoms,[23,24] providing that they met other criteria for enrollment.

When considering the addition of a medication to treat insomnia disorder in individuals with comorbid depression or anxiety symptoms, it is important to note that individuals with untreated depression or anxiety may respond differently (efficacy and adverse event profile) than individuals without depression or anxiety and without medications used to treat these conditions. The Study 303 dataset, which includes subjects with a history of depression or anxiety symptoms, provides the opportunity to study concomitant use of a medication (LEM) in those who were also actively treated with medications for symptoms of depression or anxiety. The purpose of this post hoc analysis was to evaluate LEM use in those treated concomitantly with medications for depression or anxiety symptoms and to provide a preliminary indication of the effects of LEM in subjects with treated depression or anxiety symptoms.

2 | METHODS

2.1 | Study design

Study 303 was a 12-month, phase 3, global (Canada, Finland, Germany, Italy, Japan, Korea, New Zealand, Poland, Romania, Spain, Mexico, and the United States), multicenter, randomized, placebo-controlled (for first 6 months), double-blind, 2-dose, parallel-group study conducted between November 15, 2016, and January 8, 2019.[23] The 6-month placebo-controlled period ended on May 31, 2018. After a 2-week placebo run-in period, subjects ($N = 949$) were randomized (1:1:1) to placebo, LEM5, or LEM10 for 6 months (Treatment Period 1). For the second 6 months (Treatment Period 2), subjects from the placebo arm were re-randomized (1:1) to LEM5 or LEM10, and subjects previously receiving LEM continued to receive LEM at their original dose; data from Treatment Period 2 are not included here. Complete study details were previously reported.[23]

The study protocol was approved by relevant institutional review boards and independent ethics committees. Protocol amendments were approved where appropriate before implementation. The study adhered to Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations. All study subjects provided written informed consent prior to screening.

2.2 | Subjects

Complete study inclusion and exclusion criteria were reported previously.[23] Briefly, the subjects were adults ≥18 years of age with insomnia disorder per DSM-5.[25] Subjects were required to have an ISI score[26] ≥ 15, a history of subjective sleep onset latency (sSOL) ≥30 min, and/or subjective wake after sleep onset (sWASO) ≥60 min at least 3 times a week in the 4 weeks before enrollment.[23] These criteria were confirmed by sleep history, questionnaires, and sleep diaries. Subjects with sleep disorders other than insomnia were excluded. Subjects with medical and psychiatric conditions, including mild depression and anxiety symptoms, were permitted if their condition was stable, adequately controlled, and not treated with a prohibited medication. Prohibited medications included strong and moderate cytochrome P450 CYP3A inhibitors and all CYP3A inducers, pharmacologic or nonpharmacologic treatment for insomnia disorder, medications used for the purpose of inducing sleep (hypnotics) or inducing wakefulness (stimulants; except caffeine), and medications with known sedating effects or alerting effects. Depression and anxiety were assessed using the Beck Depression Inventory-II (BDI-II)[27] and Beck Anxiety Inventory (BAI),[28] respectively, at screening only. Subjects with depression or anxiety symptoms (with or without a formal diagnosis of MDD or anxiety disorder) were eligible to participate in this study provided that they had BDI-II scores <19 and BAI scores <15, were not on any prohibited medications, and their condition did not affect their safety or interfere with the study assessments. The protocol did not define specific inclusion/exclusion criteria for the Fatigue Severity Scale (FSS).[29]

The analysis subgroup comprised subjects from the full analysis set (FAS) with a medical history of comorbid depression or anxiety symptoms who were treated with a concomitant medication for depression or anxiety during the study (referred to as "subpopulation"). The FAS was defined as randomized subjects who received ≥1 dose of a randomized study drug and had ≥1 post-dose primary efficacy measurement.

2.3 | Assessments

Subjects completed an electronic sleep diary each day within 1 h of morning awakening throughout the study and beginning during

the Screening Period.[23] Changes from baseline (CFB) (Study Day 1) in subjective sleep parameters were assessed after the first 7 nights and for the last 7 nights at the end of each month. sSOL was the estimated time (minutes) from when the subject attempted to sleep until sleep onset. sWASO was the estimated sum of time (minutes) of wakefulness during the night after initial sleep onset until the time that the subject stopped trying to sleep for the night. Subjective total sleep time (sTST) was the minutes spent asleep from sleep onset until the subject stopped trying to sleep for the night. Subjective sleep efficiency (sSE) was the proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reported attempting to sleep until the time the subject stopped trying to sleep for the night, and time spent asleep derived from time spent in bed minus sWASO total time spent asleep divided by time in bed.

In Treatment Period 1, the ISI and FSS were assessed at baseline (Study Day 1), Month 1, Month 3, and Month 6. CFB in ISI total score[26] (items 1–7) and FSS total score[29] were also evaluated at the end of Months 1, 3, and 6. The ISI is a 7-item questionnaire that assesses the daytime and nighttime impact and severity of insomnia symptoms. Each item is assessed on a 5-point Likert scale ranging from 0 (no problem) to 4 (very severe problem), yielding a maximum total score of 28. 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. The FSS is a 9-item self-report questionnaire used to assess subjects' level of agreement with statements about the impact of fatigue on their daily functioning and quality of life. Subjects rated 9 statements about fatigue on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree) yielding a maximum score of 63. Higher scores indicate more fatigue.

Adverse events were recorded throughout the study.

2.4 | Data analysis

CFB in subjective sleep parameters (sSOL [log-transformed], sSE, sWASO, and sTST) and ISI and FSS total scores were calculated using a mixed-effect repeated-measurement analysis with age group, region, treatment, visit (time point), and treatment-by-visit interaction as fixed effects and baseline sleep diary value as a covariate. CFB are reported as least squares geometric means (LSGM: sSOL) and least squares means (LSM visit estimate: sSE, sWASO, and sTST). For sSOL, sWASO, and sSE, missing values were imputed using multiple imputations and assumed to be missing not at random. For sTST, ISI, and FSS, missing values were not imputed and were assumed to be missing at random.

Safety outcomes are reported using descriptive statistics (Treatment Period 1 only). The post hoc analyses in this subgroup were not powered to demonstrate between-group treatment differences.

The *p*-value cut-off was 0.05. There were no adjustments for multiple tests.

3 | RESULTS

3.1 | Subject disposition and demographics

Of the 949 subjects in the Study 303 FAS,[23] 61 (6.4%) subjects with histories of comorbid symptoms of depression and/or anxiety and who were taking concomitant medication indicated in such disorders were included in this analysis (placebo 5.0% [16 of 318 in the FAS], LEM5 6.6% [21 of 316], LEM10 7.6% [24 of 315]). A total of 48 (78.7%) subjects in the subpopulation completed Treatment Period 1 (Figure 1). Like the randomized population,[23] most discontinuations occurred from the LEM10 group.

In the subpopulation, baseline demographics, disease characteristics, and sleep measures were generally well balanced across treatment groups (Table 1). However, sWASO was numerically higher (worse) in the LEM5 group compared with the placebo and LEM10 treatment groups, and sTST was numerically higher (better) in the LEM10 group compared with the placebo and LEM5 treatment groups. There was a higher proportion of females in the subpopulation (Table 1) compared with the FAS.[23] Baseline BDI-II and BAI scores were higher in the subpopulation (Table 1) compared with the FAS.

3.2 | Concomitant use of medications in subjects treated for mood and anxiety disorders

Approximately 80% of subjects maintained constant permitted concomitant depression or anxiety medication use throughout Treatment Period 1; the remaining subjects stopped or started concomitant medication during the study, started concomitant medication after the first LEM dose and continued after the last LEM dose, or started concomitant medication prior to and stopped before the last LEM dose (Table 2). Medication patterns were generally similar across treatment groups. The most used concomitant medication in each treatment arm was the SSRI escitalopram, which was taken by 19 subjects overall. The SNRI venlafaxine (10 subjects) and another SSRI sertraline (8 subjects) were the second and third most taken concomitant medications. Aripiprazole, which is an atypical antipsychotic, was taken by 2 subjects in the LEM10 group. Most of the remaining subjects took another type of SSRI or SNRI. Because this was a multinational study, country-specific prescribing practices likely influenced the types of concomitant medications taken during Study 303.

3.3 | Subjective sleep parameters

In the subpopulation, sSOL decreased from baseline at each time point during Treatment Period 1 in the placebo and LEM treatment groups (Table 3). Month 6 decreases from baseline in sSOL (per LSGM treatment ratios) were larger for both LEM treatment groups compared with placebo (Figure 2A). Likewise, sWASO decreased

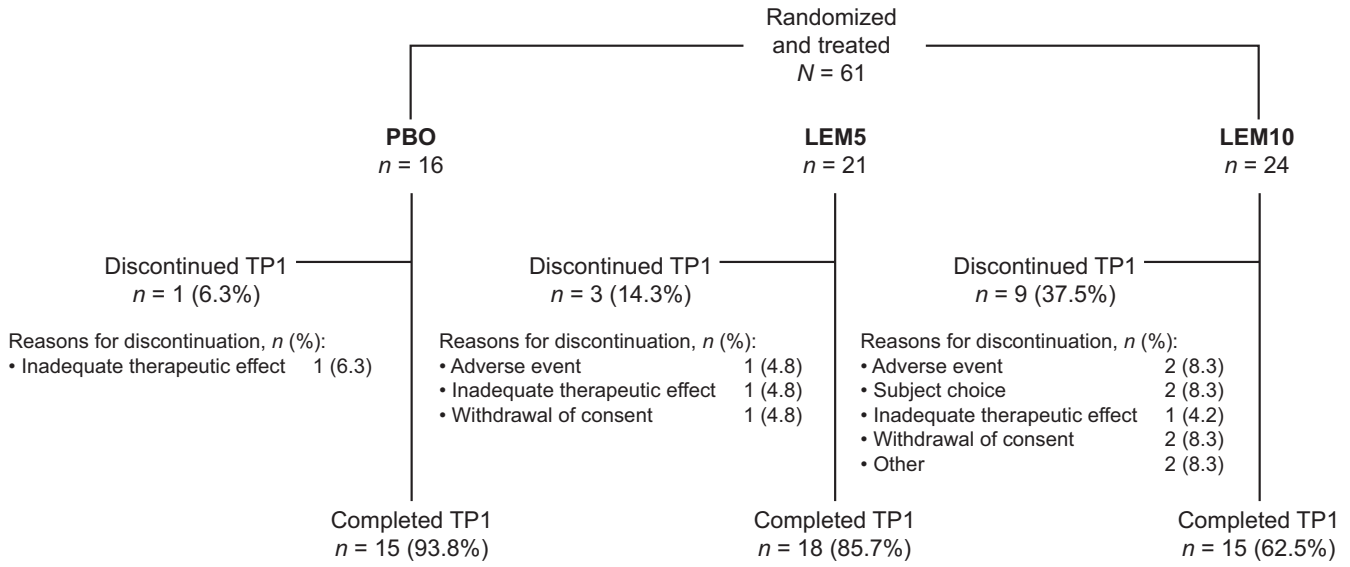

FIGURE 1 Disposition of subjects treated for depression or anxiety symptoms in Study 303 treatment period. Figure adapted from Dash, et al. under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). LEM10, lemborexant 10 mg; LEM5, lemborexant 5 mg; PBO, placebo; TP1, Treatment Period 1.

over the course of Treatment Period 1 in the placebo and LEM treatment groups in the subpopulation (Table 3). Month 6 decreases from baseline in sWASO (per LSM treatment differences) were similar between the LEM treatment groups and placebo (Figure 2B).

Both sSE and sTST increased over the course of Treatment Period 1 in the placebo and LEM treatment groups in the subpopulation (Table 3). The Month 6 increases from baseline in sSE and sTST (per LSM treatment differences) were larger for both LEM treatment groups compared with placebo (Figure 2C,D).

Month 6 outcomes (favoring LEM) for sSOL, sSE, and sTST in the subpopulation were generally consistent with outcomes observed in the FAS, whereas decreases from baseline in sWASO relative to placebo were less pronounced in the subpopulation (Figure 2).[23,30] Responses in the placebo-treated subjects were greater among those in the subpopulation compared with the FAS (Table 3).[23,30]

3.4 | Insomnia severity index

In the subpopulation, ISI total scores decreased over Treatment Period 1 in all treatment groups (Table 3 and data not shown). The Month 6 decrease from baseline in ISI total score (per LSM treatment differences) was larger for LEM5 compared with placebo, but similar between LEM10 and placebo and was less pronounced compared with the FAS (Table 3; Figure 2E).

3.5 | Fatigue severity scale

FSS total scores decreased over Treatment Period 1 in the placebo and LEM5 groups in the subpopulation (Table 3). Month 6 decreases from baseline in FSS total scores (LSM treatment differences) were larger for placebo compared with both LEM treatment groups, whereas Month 6 decreases from baseline were smaller for placebo than for both LEM treatment groups in the FAS (Table 3; Figure 2F). A greater placebo response in the subpopulation (Table 3) resulted in Month 6 FSS outcomes favoring placebo, whereas Month 6 FSS outcomes in the FAS favored LEM (Figure 2F).[31]

3.6 | Safety

In the subpopulation, the incidences of any treatment-emergent adverse event (TEAEs) and any serious TEAEs were generally similar between LEM treatment groups (Table 4). The incidence of treatment-related TEAEs was higher with LEM compared with placebo, but the number of subjects with TEAEs was very low. In the subpopulation, fall, contusion, and headache were among the most common TEAEs; somnolence was reported by 3 subjects in the LEM10 group. Findings in the subpopulation were generally consistent with the safety analysis set (Table 4).[23]

4 | DISCUSSION

This analysis evaluated the effects of a dual orexin receptor antagonist, LEM, in subjects with insomnia disorder who were treated with concomitant medication for mild symptoms of depression or anxiety disorder. Notably, the findings from this post hoc analysis of Study 303 revealed that subjects with insomnia disorder who were treated with LEM as an add-on to their therapeutic regimen for depression or anxiety symptoms exhibited improvements in all sleep outcomes over the first 6 months of the study. Improvements in sleep outcomes in the subpopulation were directionally similar to

TABLE 1 Summary of Baseline Demographics and Baseline Sleep Measures in Subjects Treated for Depression or Anxiety Symptoms and the Full Analysis Set (Treatment Period 1).

	Subjects treated for depression or anxiety symptoms			Full analysis set[a,b]		
	PBO (*n* = 16)	LEM5 (*n* = 21)	LEM10 (*n* = 24)	PBO (*n* = 318)	LEM5 (*n* = 316)	LEM10 (*n* = 315)
Age, years						
Mean (SD)	56.2 (15.1)	53.4 (12.5)	52.1 (12.9)	54.5 (14.0)	54.2 (13.7)	54.8 (13.7)
Median (range)	63 (25–72)	55 (24–72)	55 (19–74)	56.0 (18–83)	55.0 (20–85)	55.0 (18–88)
Sex, *n* (%)						
Male	2 (12.5)	1 (4.8)	5 (20.8)	102 (32.1)	107 (33.9)	93 (29.5)
Female	14 (87.5)	20 (95.2)	19 (79.2)	216 (67.9)	209 (66.1)	222 (70.5)
Race, *n* (%)						
White	12 (75.0)	17 (81.0)	17 (70.8)	232 (73.0)	222 (70.3)	225 (71.4)
Black	1 (6.3)	2 (9.5)	2 (8.3)	23 (7.2)	27 (8.5)	26 (8.3)
Asian[c]	2 (12.5)	2 (9.5)	5 (20.8)	59 (18.6)	61 (19.3)	58 (18.4)
Other[d]	1 (6.3)	0	0	4 (1.3)	6 (1.9)	6 (1.9)
BMI, mean (SD), kg/m^2	28.6 (6.2)	31.6 (7.5)	27.9 (5.5)	27.2 (5.5)	27.3 (6.3)	27.2 (5.6)
BDI-II score, mean (SD)	7.6 (4.7)	5.1 (4.2)	5.8 (5.6)	3.8 (4.2)	3.9 (4.2)	4.1 (4.3)
BAI score, mean (SD)	2.8 (2.6)	3.6 (3.3)	4.1 (3.5)	2.3 (3.1)	2.5 (3.1)	2.6 (3.1)
ISI Total Score, mean (SD)	18.2 (3.1)	19.8 (3.2)	17.6 (4.8)	19.0 (3.1)	19.6 (3.3)	19.1 (3.4)
FSS Total Score, mean (SD)	43.3 (10.5)	42.6 (10.8)	41.5 (13.6)	35.2 (13.6)	37.4 (12.7)	36.0 (13.0)
Subjective sleep parameters						
sSOL, median (1st and 3rd quartiles), min	62.1 (42.9, 105.7)	60.0 (42.2, 75.0)	59.3 (41.6, 108.9)	55.9 (34.1, 78.9)	53.6 (32.9, 75.7)	55.7 (33.6,85.1)
sSE, mean (SD), %	62.9 (18.0)	60.8 (19.5)	66.7 (14.6)	61.3 (17.8)	63.1 (18.2)	62.0 (17.3)
sWASO, mean (SD), min	107.2 (71.9)	133.9 (81.0)	109.4 (71.4)	132.5 (80.2)	132.8 (82.5)	136.8 (87.4)
sTST, mean (SD), min	317.9 (100.5)	307.3 (103.2)	348.2 (79.6)	304.3 (91.5)	315.5 (93.5)	306.9 (88.0)

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; BMI, body mass index; FSS, Fatigue Severity Scale; ISI, Insomnia Severity Index; LEM10, lemborexant 10 mg; LEM5, lemborexant 5 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]Portions of these data were published in Kärppä M, et al. Sleep. 2020;43 (9), Chepke C, et al. Postgrad Med. 2022;134 (3):316–25, and Yardley, et al. Sleep Medicine. 2021: 333–342.

[b]Full analysis set defined as randomized subjects who received ≥1 dose of randomized study drug and had ≥1 post-dose primary efficacy measurement.

[c]Includes Japanese, Chinese, and other Asian.

[d]Includes American Indian or Alaska native, Native Hawaiian or other Pacific Islander, and other.

TABLE 2 Concomitant Medication Use in Subjects Treated for Depression or Anxiety Symptoms.

	PBO ($n=16$)	LEM5 ($n=21$)	LEM10 ($n=24$)
Concomitant medication use pattern, *n* (%)[a]			
Stopped and started during study	1 (6.3)	2 (9.5)	2 (8.3)
Constant	13 (81.3)	17 (81.0)	18 (75.0)
Started after first dose and continued after last dose of LEM	3 (18.8)	3 (14.3)	5 (20.8)
Started prior and stopped before last dose of LEM	3 (18.8)	5 (23.8)	4 (16.7)
Concomitant medications used during study, *n*[a]			
Serotonin1A agonists			
Buspirone	0	0	1
Tandospirone	0	1	0
Carbonic anhydrase inhibitor			
Topiramate	0	0	1
Noradrenergic and serotonergic antagonist			
Mirtazapine	0	0	1
Norepinephrine–dopamine reuptake inhibitor			
Bupropion	0	0	1
Serotonin antagonist and reuptake inhibitor			
Trazodone[b]	1	1	2
Vortioxetine	1	1	0
Dopamine partial agonist			
Aripiprazole	0	0	2
Serotonin and norepinephrine reuptake inhibitor			
Duloxetine	1	1	3
Venlafaxine	2	4	4
Selective serotonin reuptake inhibitor			
Citalopram	3	2	1
Escitalopram	7	5	7
Fluoxetine	1	1	0
Paroxetine	0	1	5
Sertraline	2	6	0
Tricyclic medication			
Amitriptyline	1	0	0
Nortriptyline	0	0	1
Tianeptine	0	2	0

Abbreviations: LEM, lemborexant; LEM10, lemborexant 10 mg; LEM5, lemborexant 5 mg; PBO, placebo.

[a]Subjects can be counted in multiple rows based on having different medications that were stopped, started, and/or constant.

[b]Medication not permitted by study protocol.

those observed in the FAS.[30,31] In general, improvements in sleep parameters with LEM relative to placebo were less pronounced in the subpopulation compared with the FAS[30,31] because there was a greater placebo response for these variables in the subjects treated for symptoms of depression or anxiety; however, the numerical magnitude of CFB within the active treatment groups was generally similar between the subpopulation and the FAS.[30,31]

The reason for the greater placebo group response in the subpopulation compared with the FAS is unknown. While the subjects did not meet criteria for MDD at the time of the study, the placebo responses of individuals with MDD reportedly can be quite large.[32,33] One review of randomized clinical trials involving adults with MDD showed that 29.7% (range 12.5%–51.8%) of subjects met criteria for therapeutic response to placebo.[33] Similarly, in randomized clinical

TABLE 3 Change From Baseline in Subjective Sleep Parameters, ISI, and FSS in Subjects Treated for Depression or Anxiety Symptoms in the Full Analysis Set (Treatment Period 1).

	Subjects treated for depression or anxiety symptoms			Full analysis set[a,b]		
	PBO ($n=16$)	LEM5 ($n=21$)	LEM10 ($n=24$)	PBO ($n=318$)	LEM5 ($n=316$)	LEM10 ($n=315$)
sSOL						
Baseline, median (1st and 3rd quartiles), minutes	62.1 (42.9, 105.7)	60.0 (42.2, 75.0)	59.3 (41.6, 108.9)	55.9 (34.1, 78.9)	53.6 (32.9, 75.7)	55.7 (33.6, 85.1)
Change from baseline, median (1st and 3rd quartiles), minutes						
First 7 nights	−16.8 (−35.0, 10.5)	−12.9 (−42.1, 7.8)	−18.7 (−34.0, −11.4)	−3.0 (−17.1, 7.9)	−11.0 (−28.0, 0.0)	−12.2 (−31.0, −0.5)
Month 1	−21.8 (−39.6, 0.2)	−8.8 (−42.9, 4.3)	−25.3 (−51.2, −7.6)	−7.1 (−25.7, 3.6)	−13.7 (−35.0, −1.0)	−19.9 (−36.4, −3.6)
Month 3	−23.7 (−45.7, 0.0)	−28.1 (−75.7, 1.4)	−31.0 (−58.7, −18.0)	−11.3 (−27.9, 1.4)	−20.7 (−41.5, −6.1)	−25.7 (−46.6, −4.7)
Month 6	−23.2 (−44.3, −5.0)	−22.8 (−78.6, −6.4)	−32.1 (−47.1, −17.7)	−11.4 (−33.6, 0.0)	−21.8 (−44.3, −11.1)	−28.2 (−54.4, −9.3)
sWASO						
Baseline, mean (SD), minutes	107.2 (71.9)	133.9 (81.0)	109.4 (71.4)	132.5 (80.2)	132.8 (82.5)	136.8 (87.4)
Change from baseline, LSM visit estimate (SE), minutes						
First 7 nights	−7.6 (9.8)	−23.9 (9.6)	−6.4 (9.6)	−4.8 (2.7)	−19.1 (2.8)	−21.5 (2.7)
Month 1	−14.8 (12.5)	−19.7 (11.7)	−4.5 (11.7)	−17.2 (3.1)	−22.7 (3.1)	−24.2 (3.1)
Month 3	−22.5 (15.1)	−42.9 (14.1)	−23.5 (14.0)	−26.8 (3.3)	−40.3 (3.4)	−36.9 (3.4)
Month 6	−39.5 (13.5)	−39.6 (12.7)	−41.1 (13.2)	−29.3 (3.6)	−46.8 (3.7)	−41.9 (3.7)
sSE						
Baseline, mean (SD), %	62.9 (18.0)	60.8 (19.5)	66.7 (14.6)	61.3 (17.8)	63.1 (18.2)	62.0 (17.2)
Change from baseline, LSM visit estimate (SE), %						
First 7 nights	3.5 (2.2)	9.9 (2.2)	6.1 (2.2)	2.1 (0.6)	6.4 (0.6)	7.9 (0.7)
Month 1	7.2 (3.0)	10.1 (2.8)	8.2 (2.8)	5.5 (0.7)	7.8 (0.7)	9.2 (0.8)
Month 3	8.9 (3.8)	17.1 (3.5)	12.7 (3.5)	8.6 (0.8)	12.8 (0.8)	12.9 (0.8)
Month 6	14.2 (3.7)	16.6 (3.4)	17.7 (3.5)	9.6 (0.8)	14.2 (0.9)	14.3 (0.9)
sTST						
Baseline, mean (SD), minutes	317.9 (100.5)	307.3 (103.2)	348.2 (79.6)	304.3 (91.5)	315.5 (93.5)	306.9 (88.0)
Change from baseline, LSM visit estimate (SE), minutes						
First 7 nights	11.7 (11.4)	56.1 (11.4)	35.1 (11.5)	11.4 (3.3)	33.4 (3.3)	43.2 (3.3)
Month 1	31.8 (16.2)	58.9 (15.2)	50.9 (15.0)	27.5 (3.9)	39.2 (3.9)	50.0 (4.0)
Month 3	37.5 (19.6)	87.9 (18.1)	79.5 (18.0)	46.4 (4.3)	63.8 (4.4)	68.1 (4.4)
Month 6	67.1 (19.6)	97.0 (18.1)	100.0 (18.8)	51.4 (4.6)	70.0 (4.7)	74.1 (4.8)
ISI total score						
Baseline, mean (SD)	18.2 (3.1)	19.8 (3.2)	17.6 (4.8)	19.0 (3.1)	19.6 (3.3)	19.0 (3.4)

TABLE 3 (Continued)

	Subjects treated for depression or anxiety symptoms			Full analysis set[a,b]		
	PBO ($n = 16$)	LEM5 ($n = 21$)	LEM10 ($n = 24$)	PBO ($n = 318$)	LEM5 ($n = 316$)	LEM10 ($n = 315$)
Change from baseline, LSM visit estimate (SE)						
Month 1	−4.5 (1.3)	−5.5 (1.4)	−5.3 (1.4)	−5.4 (0.3)	−6.9 (0.3)	−7.3 (0.4)
Month 3	−5.7 (1.6)	−7.4 (1.6)	−8.5 (1.6)	−6.3 (0.4)	−8.3 (0.4)	−8.9 (0.4)
Month 6	−7.9 (1.5)	−8.8 (1.5)	−7.6 (1.5)	−7.4 (0.4)	−9.5 (0.4)	−9.7 (0.4)
FSS total score						
Baseline, mean (SD)	43.3 (10.5)	42.6 (10.8)	41.5 (13.6)	35.2 (13.6)	37.4 (12.7)	36.0 (13.0)
Change from baseline, LSM visit estimate (SE)						
Month 1	−3.7 (2.7)	−4.3 (2.8)	−2.9 (2.8)	−4.4 (0.7)	−6.0 (0.7)	−6.4 (0.7)
Month 3	−11.4 (3.4)	−4.1 (3.3)	−6.8 (3.4)	−4.8 (0.7)	−7.0 (0.7)	−7.8 (0.7)
Month 6	−11.9 (3.1)	−7.1 (3.1)	−3.0 (3.3)	−6.4 (0.8)	−8.9 (0.8)	−9.0 (0.8)

Abbreviations: FSS, fatigue severity score; ISI, Insomnia Severity Index; LEM10, lemborexant 10 mg; LEM5, lemborexant 5 mg; LSM, least squares mean; PBO, placebo; SD, standard deviation; SE, standard error; sSE, subjective sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.

[a]Portions of these data were published in Kärppä M, et al. Sleep. 2020;43 (9), Chepke C, et al. Postgrad Med. 2022;134 (3):316–25, and Yardley, et al. Sleep Medicine. 2021: 333–342.

[b]Full analysis set defined as randomized subjects who received ≥1 dose of randomized study drug and had ≥1 post-dose primary efficacy measurement.

trials, large placebo effects are frequently reported in subjects with insomnia disorder who are randomized to placebo.[34–36] The placebo response in our analysis could also reflect the small sample size and large error margins. Additionally, it is possible that concomitant background therapy with antidepressant or anxiolytic action may have had a beneficial effect on sleep parameters (either directly or indirectly by improving the associated conditions) in the placebo and LEM groups. Such a beneficial effect could reduce the apparent treatment effect size of add-on LEM, a finding previously observed in individuals with insomnia and comorbid MDD or GAD who were treated with eszopiclone and SSRIs.[37]

In the subpopulation, the CFB in ISI was similar between both treatment groups and the placebo group; however, relative changes among groups were small. For the FSS, the numerical changes were largest in the placebo group, followed by LEM5 and LEM10. For both measures, these findings likely reflect the small sample size and correspondingly wide error ranges. Similarly, although the difference in FSS scores between the placebo and LEM10 groups appears large, the confidence intervals overlap substantially. In addition to the small sample sizes, another factor responsible for the observed finding may be that the concomitant drugs (mostly SSRIs and SNRIs) may have improved fatigue in the subpopulation, including those in the placebo group, thereby decreasing the benefit of LEM on the FSS versus placebo.

There were no new safety signals or increased rates of TEAEs in these subjects compared with the overall study population.[23] It should be noted, however, that some antidepressants, such as fluvoxamine, which is a moderate CYP3A4 inhibitor,[38] should not be used with LEM or may require dose adjustment because of the impact on the pharmacokinetics of LEM or the co-medication itself. In a physiologically based pharmacokinetic modeling analysis, LEM demonstrated weak drug–drug interaction with fluoxetine (weak CYP3A inhibitor), which was predicted to increase LEM exposure by less than 2-fold.[39] Additionally, in a phase 1 study, LEM coadministration reduced bupropion (CYP2B6 substrate) exposure by approximately 0.5-fold.[40]

A strength of this analysis is that it provides preliminary evidence on the efficacy and safety of add-on therapy with a dual orexin receptor antagonist in subjects with insomnia disorder who are taking pharmacological treatment for mild symptoms of depression or anxiety. It is unclear whether these medications for the treatment of mild depression or anxiety symptoms themselves influenced sleep in this subject population; further studies are needed to determine their impact, if any, on sleep parameters. The analyses are limited by the small sample size since that size did not have enough power to demonstrate between-group treatment differences. Thus, definite conclusions regarding LEM efficacy and/or safety in this subgroup of subjects cannot be made. Further, this analysis was not powered to detect statistically significant differences between the subpopulation and the FAS. This study had a fixed-dose design such that treatment was not optimized for each subject. In addition, depression and anxiety symptoms were only assessed at baseline, so effects of LEM on depression or anxiety severity and symptoms during treatment could not be ascertained.

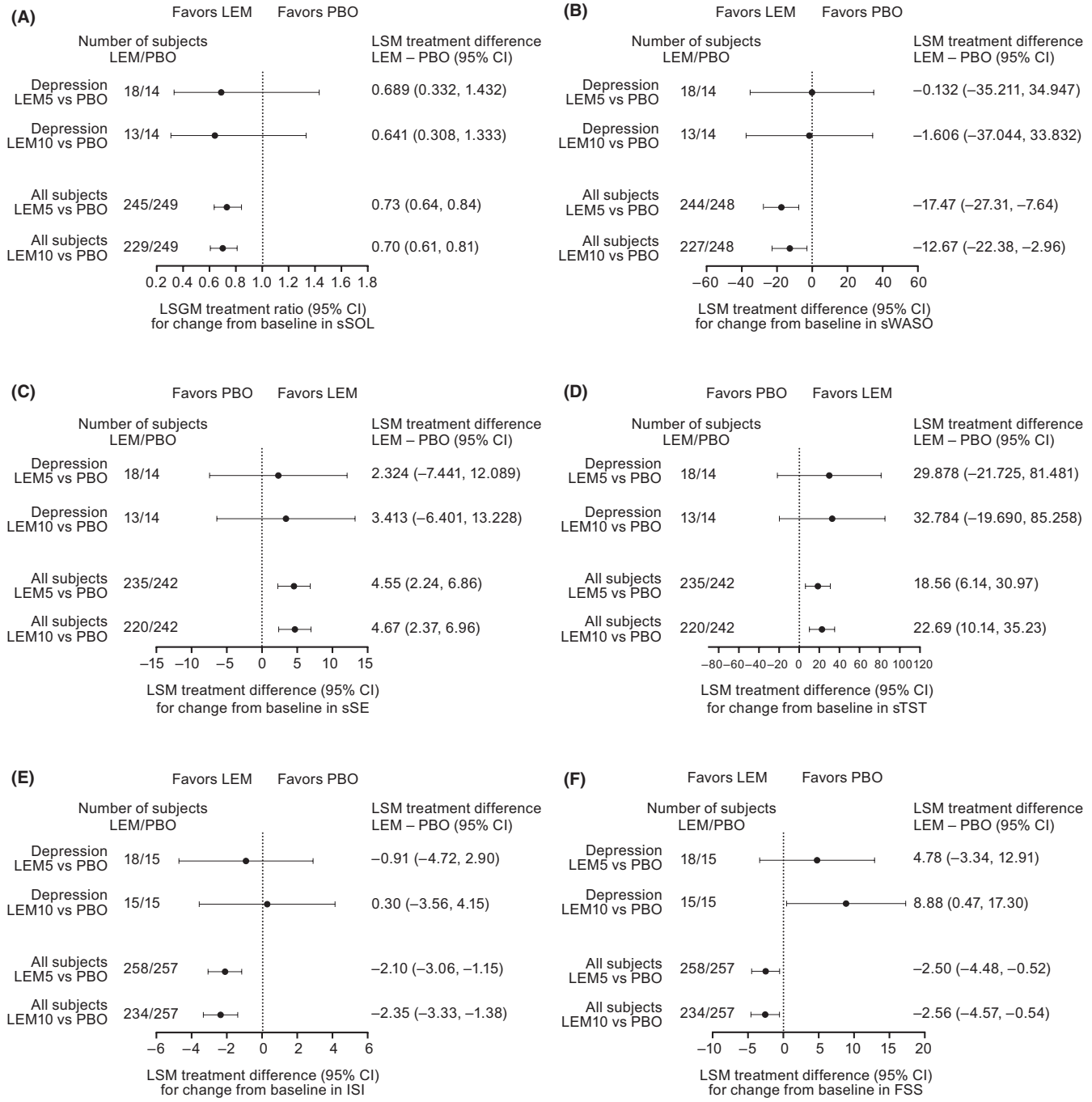

FIGURE 2 Forest plots showing the LSGM treatment ratio or LSM treatment difference for the change from baseline in (A) sSOL, (B) sWASO, (C) sSE, (D) sTST, (E) ISI, and (F) FSS total scores at Month 6 in subjects treated for depression or anxiety symptoms. Data for all subjects were previously published in Dash A, et al. Sleep Med X. 2022;4:100044, Kärppä M, et al. Sleep. 2020;43 (9), and Chepke C, et al. Postgrad Med. 2022;134 (3):316–25 and are provided for comparative purposes. Figure adapted from Dash, et al. under the CCBY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). CI, confidence interval; FSS, fatigue severity score; ISI, Insomnia Severity Index; LEM10, lemborexant 10 mg; LEM5, lemborexant 5 mg; LSGM, least squares geometric means; LSM, least squares mean; PBO, placebo; SE, sleep efficiency; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.

5 | CONCLUSION

The findings of this post hoc analysis of Study 303 show that LEM add-on therapy benefited subjects with chronic insomnia who were concomitantly taking a medication with antidepressant/anxiolytic activity, with no new safety signals or concerns. These results warrant future investigation with larger studies focused on a subject population with insomnia and comorbid MDD or anxiety disorder. Further studies are also needed to determine if LEM therapy for insomnia has ameliorative effects on depression and anxiety severity and symptoms or mitigates risks of depression relapse.

TABLE 4 Summary of Safety in Treatment Period 1 of Study 303 in Subjects Treated for Depression or Anxiety Symptoms.

	Subjects treated for depression or anxiety symptoms			Safety analysis set[a]		
	PBO (*n* = 16)	LEM5 (*n* = 21)	LEM10 (*n* = 24)	PBO (*n* = 319)	LEM5 (*n* = 314)	LEM10 (*n* = 314)
General category of events, *n* (%)						
Any TEAE	13 (81.3)	15 (71.4)	13 (54.2)	200 (62.7)	192 (61.1)	187 (59.6)
Treatment-related TEAE	2 (12.5)	4 (19.0)	7 (29.2)	44 (13.8)	78 (24.8)	91 (29.0)
Severe TEAE	1 (6.3)	2 (9.5)	2 (8.3)	10 (3.1)	13 (4.1)	8 (2.5)
Serious TEAE	1 (6.3)	1 (4.8)	2 (8.3)	5 (1.6)	7 (2.2)	9 (2.9)
TEAE leading to study dose adjustment	0	2 (9.5)	3 (12.5)	18 (5.6)	25 (8.0)	33 (10.5)
TEAE leading to study drug discontinuation	0	1 (4.8)	2 (8.3)	12 (3.8)	13 (4.1)	26 (8.3)
TEAE leading to study dose interruption	0	1 (4.8)	2 (8.3)	7 (2.2)	13 (4.1)	8 (2.5)
TEAEs occurring in ≥2 subjects in any treatment group among subjects treated for depression or anxiety, *n* (%)						
Fall	2 (12.5)	1 (4.8)	3 (12.5)	10 (3.1)	5 (1.6)	5 (1.6)
Contusion	3 (18.8)	1 (4.8)	1 (4.2)	4 (1.3)	2 (0.6)	3 (1.0)
Headache	0	3 (14.3)	2 (8.3)	21 (6.6)	28 (8.9)	21 (6.7)
Dizziness	2 (12.5)	0	2 (8.3)	6 (1.9)	5 (1.6)	4 (1.3)
Urinary tract infection	1 (6.3)	2 (9.5)	1 (4.2)	7 (2.2)	4 (1.3)	9 (2.9)
Nasopharyngitis	3 (18.8)	1 (4.8)	1 (4.2)	40 (12.5)	30 (9.6)	29 (9.2)
Back pain	0	2 (9.5)	1 (4.2)	8 (2.5)	12 (3.8)	9 (2.9)
Edema peripheral	1 (6.3)	2 (9.5)	0	2 (0.6)	5 (1.6)	0
Somnolence	0	0	3 (12.5)	5 (1.6)	27 (8.6)	41 (13.1)
Musculoskeletal chest pain	2 (12.5)	0	0	4 (1.3)	0	0
Anxiety	0	2 (9.5)	0	3 (0.9)	4 (1.3)	1 (0.3)
Musculoskeletal pain	0	0	2 (8.3)	0	1 (0.3)	4 (1.3)

Abbreviations: LEM10, lemborexant 10 mg, LEM5, lemborexant 5 mg; PBO, placebo; TEAE, treatment-emergent adverse event.

[a]Portions of these data were published in Kärppä M, et al. Sleep. 2020;43 (9) and Yardley, et al. Sleep Medicine. 2021: 333–342.

AUTHOR CONTRIBUTIONS

Andrew Krystal: Writing; approval of final version. Pierre Blier: Writing; approval of final version. Larry Culpepper: Writing; approval of final version. Andrew A. Nierenberg: Writing; approval of final version. Yoshikazu Takaesu: Writing; approval of final version. Naoki Kubota: Conception; methodology; writing; approval of final version. Margaret Moline: Conception; methodology; resources; writing; approval of final version. Manoj Malhotra: Writing; approval of final version. Kate Pinner: Analysis; writing; approval of final version. Jane Yardley: Writing; approval of final version.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Luke Carey, PhD, CMPP, and Lori Kornberg, PhD, of Envision Pharma Group, and editorial support was provided by Carla Resvanis of OPEN Health Group. Both were funded by Eisai Inc. Envision Pharma's services complied with international guidelines for Good Publication Practice (GPP2022). We thank Elizabeth Pappadopulos for her contributions to the conception and design of this work, as well as for reviewing and revising earlier drafts of this manuscript.

FUNDING INFORMATION

The research in this manuscript was supported by Eisai Inc. The investigators retained full independence in the conduct of this research.

CONFLICT OF INTEREST STATEMENT

AK received consulting fees from Adare, Axsome Therapeutics, Big Data, Eisai Inc., Evecxia Therapeutics, Ferring Pharmaceuticals, Galderma, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Merck, Millennium Pharmaceuticals, Neurocrine Biosciences, Otsuka Pharmaceutical, Pernix Therapeutics, Sage Therapeutics, and Takeda; has received grant or research support from Axsome Therapeutics, Janssen, National Institutes of Health, The Ray and Dagmar Dolby Family Fund, and Reveal Biosensors. PB has received consulting fees and received honoraria for giving lectures from AbbVie, Eisai, Janssen, Otsuka/

Lundbeck, Merck, and Pfizer; and has received grant or research support from Allergan, Canadian Institutes for Health Research, Janssen, Ontario Brain Institute, and Otsuka/Lundbeck. LC has received consulting fees from AbbVie Pharmaceuticals, Allergan Pharmaceuticals, Eisai Pharmaceuticals, Sunovion Pharmaceuticals Inc., and Supernus Pharmaceuticals; has ownership interest in M3 Information; and has received payment from Physicians Postgraduate Press as Editor-in-Chief of the *Primary Care Companion for CNS Disorders*. AAN served on advisory boards for Alkermes, Jazz Pharmaceuticals, Neuronetics, Otsuka Pharmaceutical, and Sage Therapeutics; and has received honoraria or consulting fees from Acadia Pharmaceuticals, Clexio, Eisai Inc., Janssen, Headspace Health/Ginger io, Merck, Myriad Genetics, NeuroRx, NeuroStar, Novartis, Protogenics, and Sunovion Pharmaceuticals; he holds stock options from 4 M Therapeutics, Unravel Biosciences, Inc., Altimate Health, and Flow Neurosciences, Inc. YT received grants or contracts from Otsuka Pharmaceutical, Meiji Seika Pharma, and MSD; and payment or honoraria from Eisai, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Kyowa Pharmaceutical, MSD, and Yoshitomi. NK is an employee of Eisai Co., Ltd. MMo is an employee of Eisai Inc. MMa is a former employee of Eisai Inc. KP and JY are employees of Eisai Ltd.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to intellectual property restrictions. However, the data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: The study protocol for this research was approved by a suitably constituted Ethics Committee from the institutions and it conforms to the provisions of the Declaration of Helsinki. A list of country-specific central IRBs/ERBs and local IRBs/ERBs is available upon request. The study adhered to Good Clinical Practice guidelines and local regulations.

Informed consent: All study subjects provided written informed consent prior to screening.

Registry and the registration no. of the study/trial: This trial is registered at ClinicalTrials.gov: https://classic.clinicaltrials.gov/ct2/show/NCT02952820.

Animal Studies: N/A.

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How to cite this article: Krystal A, Blier P, Culpepper L, Nierenberg AA, Takaesu Y, Kubota N, et al. Efficacy and safety of lemborexant in subjects with insomnia disorder receiving medications for depression or anxiety symptoms. Neuropsychopharmacol Rep. 2025;45:e12509. https://doi.org/10.1002/npr2.12509