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Efficacy and safety of lemborexant over 12 months in Asian adults with insomnia disorder

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ABSTRACT

Study objectives: Lemborexant (LEM) is a dual orexin receptor antagonist approved for treating adults with insomnia. We analyzed the efficacy (subjective sleep outcomes) and safety of LEM over 12 months in the subgroup of Asian subjects from Study E2006-G000-303 (Study 303).

Methods: Study 303 was a 12-month, randomized, placebo-controlled (first 6 months), double-blind, parallel-group, phase 3 study of adults with insomnia disorder. During the 6-month Period 1, subjects were randomized (1:1:1) to placebo, LEM 5 mg (LEM5), or LEM 10 mg (LEM10); LEM subjects continued treatment in the following 6-month Period 2. Outcome measures included subject-reported (subjective) sleep onset latency (sSOL), sleep efficiency (sSE), wake after sleep onset (sWASO), total sleep time (sTST), Insomnia Severity Index (ISI), and Patient Global Impression–Insomnia version (PGI-I). Treatment-emergent adverse events (TEAEs) were assessed.

Results: Overall, 178 Asian subjects (Japanese, $n = 161$; Chinese, $n = 4$; other Asian, $n = 13$) were included. Greater decreases in sSOL and sWASO and increases in sSE and sTST from baseline were observed with LEM vs placebo at 6 months; LEM benefits were sustained through 12 months. Greater decreases in ISI total score were seen with LEM vs placebo at 6 months; improvements from baseline with LEM continued through 12 months. For each PGI-I item, LEM-treated subjects had more positive medication effects than placebo-treated subjects at 6 months; these effects were maintained with LEM in Period 2. TEAEs were generally mild to moderate.

Conclusions: LEM improved subjective sleep parameters and was well-tolerated in Asian subjects with insomnia disorder over 12 months.

Clinical trial registration: ClinicalTrials.gov, NCT02952820; ClinicalTrialsRegister.eu, EudraCT Number 2015-001463-39.

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Abbreviations

AE	adverse event
BMI	body mass index
CI	confidence interval
DORA	dual orexin receptor antagonist
ISI	Insomnia Severity Index
LEM	lemborexant
LEM5	lemborexant 5 mg
LEM10	lemborexant 10 mg
LSGM	least squares geometric mean
LSM	least squares mean
MMRM	mixed-effects model of repeated measures
PBO	placebo
PGI-I	Patient Global Impression—Insomnia version
PK	pharmacokinetics
PSG	polysomnography
SD	standard deviation
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse events

1. Introduction

Insomnia is a sleep disorder involving difficulty initiating and/or maintaining sleep or early morning awakening [1]. Insomnia is a common sleep problem in Asian populations [2–6], with prevalence estimated at 8.8% [2] to 14.6% [3] in Japan, 15.0% in China [4], and 5.8% in Korea [7]. Studies in Asian countries have found that insomnia is associated with daytime dysfunction, poor physical and mental health, depression, and lower quality of life [2,3,5,6].

Pharmacologic treatments for insomnia include hypnotics, such as benzodiazepines and nonbenzodiazepine Z-drugs, melatonin receptor agonists, and some antidepressants [8,9]. However, long-term use of these medications is limited by concerns about dependence, next-day residual effects, and risk of accidents [8]. Dual orexin receptor antagonists (DORAs) target the orexin-signaling pathway involved in sleep/wake regulation [10] and have the potential to effectively treat insomnia with fewer next-day residual effects than other sleep-promoting drugs with different mechanisms of action [11,12]. Lemborexant (LEM) 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.

Two pivotal phase 3, randomized, double-blind clinical trials have demonstrated the favorable efficacy and safety profile of LEM 5 mg (LEM5) and LEM 10 mg (LEM10) in subjects with insomnia disorder [13,14]. In Study E2006-G000-304 (Study 304; SUNRISE 1; NCT02783729), LEM treatment was associated with significantly greater benefits on objective (assessed by polysomnography [PSG]) sleep measures compared with placebo (PBO) or zolpidem tartrate extended-release 6.25 mg, and on subjective measures of sleep onset and sleep maintenance vs PBO over 1 month of treatment [14].

In Study E2006-G000-303 (Study 303; SUNRISE 2; NCT02952820), which enrolled adults with insomnia disorder, LEM treatment was associated with significantly greater benefits on subjective parameters of sleep onset and sleep maintenance compared with PBO early in the study (first 7 nights) and through the end of the PBO-controlled treatment period (month 6) [13]. Improvements in subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), subjective wake after sleep onset (sWASO), and subjective total sleep time (sTST) were maintained through 12 months [15]. In addition, LEM was generally well tolerated across 12 months of treatment [15]. Most treatment-emergent adverse events (TEAEs) were rated as mild or moderate in severity; the most common TEAEs included somnolence, nasopharyngitis, and headache [13,15].

Differences in pharmacodynamics, clinical efficacy, and side effects based on race and ethnicity have been reported for various drugs, including those acting on the central nervous system [16]. A population pharmacokinetic (PK) model of LEM, based on data from 12 clinical studies, found that clearance of orally administered LEM was not meaningfully impacted by race [17]. Also, a comparison between Japanese and White subjects in a phase 1 trial (Study 003; NCT02039089) found no racial differences in pharmacokinetics, pharmacodynamics or safety [18]. In subjects receiving LEM5 or LEM10 in Study 303, the efficacy and safety of LEM treatment were similar between Japanese and non-Japanese subgroups over 6 months of treatment [19].

We report the results of a prespecified analysis of subjective sleep outcomes and safety over a longer period (12 months) in the subgroup of Asian subjects from Study 303, including subjects' perceptions of improvement in insomnia severity and medication effectiveness.

2. Methods

2.1. Study design

Full details of the methods of Study 303 have been published, including the ethical standards used in this research [13]. In brief, Study 303 was a 12-month, global, multicenter, randomized, PBO-controlled (first 6 months), double-blind, parallel-group, phase 3 study that consisted of a 6-month, PBO-controlled treatment period (Period 1; day 1 through month 6) and a second 6-month treatment period (Period 2; through month 12) that only included active treatment (Fig. 1). Both treatment periods were double-blinded.

During Period 1, subjects were randomized 1:1:1 to LEM5, LEM10, or PBO, stratified by country and age. During Period 2, subjects who received PBO in Period 1 were rerandomized (1:1; stratified by country and age) to receive LEM5 or LEM10. Subjects who received LEM5 or LEM10 during Period 1 continued on the same dose in Period 2. Period 2 findings are reported for subjects who received LEM continuously for 12 months (subjects rerandomized from PBO were not included in these analyses).

2.2. Study population

Subjects were males or females age ≥18 years who met the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria for insomnia disorder [1], with sSOL ≥30 min and/or sWASO ≥60 min occurring at least three times a week in the 4 weeks prior to enrollment and an Insomnia Severity Index (ISI) total score ≥15 at baseline. Individuals with diagnoses of comorbid sleep disorders were excluded from Study 303. Full details of study inclusion and exclusion criteria have been reported [1].

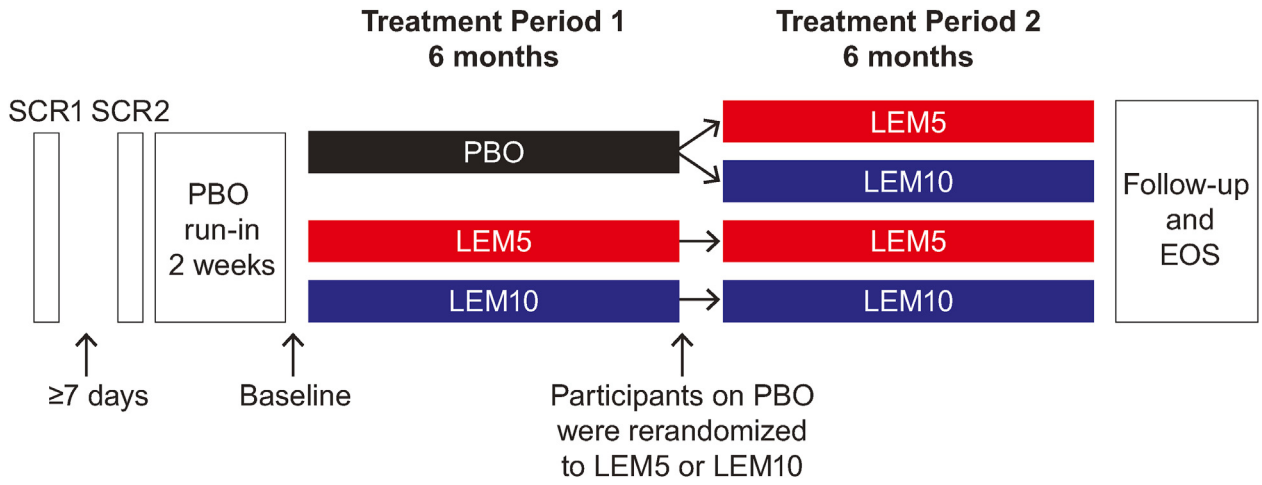

Fig. 1. Study design. In the Asian subgroup analysis, Period 2 findings are reported for subjects who received lemborexant (LEM) continuously for 12 months (subjects rerandomized from placebo [PBO] were not included in these analyses). EOS, end of study; LEM5, LEM 5 mg; LEM10, LEM 10 mg; SCR, screening. Reproduced from Yardley J et al. [15] Sleep Med. 2021;80:333–342. (https://creativecommons.org/licenses/by-nc-nd/4.0/).

The Asian subgroup included subjects who self-identified their race as Japanese, Chinese, or other Asian. These subjects were not required to be living in Asia during the study period.

2.3. Outcome measures

Efficacy endpoints for subjective sleep parameters were assessed in the Asian subgroup and overall study population using data from electronic sleep diaries completed each day within 1 h of morning awakening, beginning with screening and the placebo run-in to determine eligibility, and then throughout the 12-month study and 2-week follow-up period [13]. Endpoints included sSOL (subject-estimated time [min] from the time the subject attempted to fall asleep until sleep onset), sSE (total time spent asleep divided by time in bed, which was calculated using sleep diary entries), sWASO (subject-estimated sum of time [min] of wake during night after initial sleep onset), and sTST (derived min of sleep from sleep onset until subject stopped trying to sleep for the night).

Subjects' perceptions of their insomnia severity were assessed using the ISI. The ISI is a validated seven-item self-report questionnaire that assesses the severity of insomnia, including its impact on daytime functioning [20]. Each ISI item is rated on a 5-point Likert scale (range, 0 = no problem to 4 = very severe problem), yielding a maximum possible total score of 28. The dimensions evaluated were severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of the sleep problems by others, and distress caused by the sleep difficulties.

The Patient Global Impression–Insomnia version (PGI-I) was used to assess subjects' perceptions regarding the effects of their insomnia medication on their sleep [21,22]. Items 1–3, related to medication effects (helped/worsened sleep, decreased/increased time to fall asleep, and increased/decreased TST), were measured on a 3-point scale (1 = positive medication effect, 2 = neutral medication effect, and 3 = negative medication effect). Item 4 assessed perceived appropriateness of study medication strength and was measured on a different 3-point scale (1 = too strong, 2 = just right, and 3 = too weak).

Safety assessments for Study 303 [13] and this sub analysis included monitoring and recording TEAEs and AEs. Clinical laboratory evaluations, as well as other routine safety assessments such as electrocardiogram.

2.4. Statistical analyses

All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC) or other validated statistical software. Efficacy analyses included all randomized Asian subjects who received at least one dose of study drug and had at least one postdose primary efficacy assessment. Safety analyses included all randomized Asian subjects who received at least one dose of study drug and had at least one postdose safety assessment.

Changes from study baseline in subjective sleep parameters during Period 1 were analyzed using a mixed-effects model of repeated measures (MMRM) analysis. For sSOL, change from baseline was analyzed using MMRM analysis with log transformation of sSOL and factors for age group, treatment, visit, and treatment-by-visit interaction as fixed effects and the study baseline sSOL as a covariate. Log transformation was used for sSOL because the values were not normally distributed, and between-group differences were compared via least squares geometric means (LSGMs). For sSE, sWASO, and sTST, change from baseline was analyzed using MMRM analysis with age group, visit, (for sTST: treatment) and treatment-by-visit interaction as fixed effects and baseline value for the relevant variable as a covariate. Between-group differences were compared using least squares means (LSMs). Between-group statistical comparisons were not performed for Period 2.

Change from study baseline in ISI total score and the proportions of subjects reporting each PGI-I response were summarized descriptively for Periods 1 and 2. The Asian subgroup analyses were not controlled for multiplicity or powered for the detection of statistically significant differences.

3. Results

3.1. Baseline demographic and clinical characteristics

Full results for the overall population (n = 949) have been published [13,15]. A total of 178 subjects were included in the Asian subgroup (Table 1; Supplementary Fig. S1), comprising 18.8% of the overall study population. The majority (90.4%) of subjects in the Asian subgroup were Japanese.

The number of subjects was in balance across treatment groups. Subjects in the Asian subgroup had a mean (standard deviation [SD]) age of 51.6 (14.6) years and a mean (SD) body mass index (BMI) of 22.9 (3.5) kg/m^2, and most (57.9%) were female.

Table 1
Demographic summary for Asian subgroup (Full Analysis Set).

	PBO ($N = 59$)	LEM5 ($N = 61$)	LEM10 ($N = 58$)	Total ($N = 178$)
Age, years[a]				
Mean (SD)	53.1 (14.4)	51.3 (14.0)	50.3 (15.6)	51.6 (14.6)
Median (range)	53.0 (24–80)	50.0 (20–76)	51.0 (18–80)	51.0 (18–80)
Sex, *n* (%)				
Male	24 (40.7)	29 (47.5)	22 (37.9)	75 (42.1)
Female	35 (59.3)	32 (52.5)	36 (62.1)	103 (57.9)
Race, *n* (%)				
Japanese	54 (91.5)	53 (86.9)	54 (93.1)	161 (90.4)
Chinese	0	3 (4.9)	1 (1.7)	4 (2.2)
Other Asian	5 (8.5)	5 (8.2)	3 (5.2)	13 (7.3)
BMI, kg/m^2, mean (SD)	23.1 (3.7)	22.7 (3.2)	22.9 (3.5)	22.9 (3.5)
ISI total score, mean (SD)	17.9 (2.5)	18.1 (2.9)	18.1 (2.9)	18.0 (2.7)

[a] Age is calculated at date of informed consent.
Percentages are based on the total number of subjects with nonmissing values in the relevant treatment group.
BMI, body mass index; ISI, Insomnia Severity Index; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; SD, standard deviation.

3.2. Subjective sleep outcomes

In the subgroup of Asian subjects, results for all subjective sleep parameters (sSOL, sSE, sWASO, and sTST) favored both doses of LEM vs PBO at 6 months. The treatment benefits of LEM were maintained at 12 months (Table 2; Supplementary Fig. S2).

At 6 months, the LSGM treatment ratios showed numerically greater reductions from baseline in sSOL for both LEM groups

Table 2
Summary of subjective sleep parameters for the Asian subgroup at baseline and change from baseline at months 6 and 12 (Full Analysis Set).

	PBO ($N = 59$)	LEM5 ($N = 61$)	LEM10 ($N = 58$)
sSOL, min			
Baseline,[a] median (Q1, Q3)	49.0 (34.3, 72.9)	50.7 (35.8, 71.4)	60.0 (35.0, 90.0)
Month 6,[b] median (Q1, Q3)	31.4 (17.1, 51.4)	21.5 (13.6, 40.7)	28.2 (10.0, 42.1)
Change from baseline at month 6,[c] median (Q1, Q3)	−13.6 (−38.6, 0)	−20.7 (−37.9, −12.1)	−26.0 (−53.7, −10.0)
LSGM ratio (95% CI)[c]	0.6 (0.4, 0.7)	0.5 (0.4, 0.6)	0.4 (0.3, 0.5)
LSGM treatment ratio (95% CI)[c]		0.9 (0.7, 1.2)	0.7 (0.5, 1.0)
Month 12,[d] median (Q1, Q3)		16.4 (11.4, 34.3)	22.1 (9.3, 41.4)
Change from baseline at month 12,[e] median (Q1, Q3)		−25.7 (−45.0, −15.0)	−27.1 (−61.4, −12.9)
sSE, %			
Baseline,[f] mean (SD)	62.3 (17.7)	65.0 (18.7)	65.0 (15.7)
Month 6,[g] mean (SD)	72.7 (15.9)	80.9 (14.1)	76.0 (15.7)
Change from baseline at month 6,[h] LSM (SE)	10.5 (2.3)	14.5 (2.3)	12.8 (2.4)
Treatment difference at month 6,[h] LSM (SE)		4.0 (2.3)	2.3 (2.4)
Month 12,[i] mean (SD)		83.3 (11.6)	78.2 (13.9)
Change from baseline at month 12,[j] mean (SD)		16.1 (13.3)	15.3 (11.9)
sWASO, min			
Baseline,[a] mean (SD)	121.7 (78.5)	112.6 (78.4)	103.6 (83.1)
Month 6,[b] mean (SD)	90.5 (66.9)	61.7 (60.2)	79.7 (65.3)
Change from baseline at month 6,[c] LSM (SE)	−26.1 (9.5)	−49.6 (9.5)	−26.7 (9.9)
Treatment difference at month 6,[c] LSM (SE)		−23.4 (9.8)	−0.6 (1.0)
Month 12,[d] mean (SD)		55.2 (53.2)	74.7 (58.2)
Change from baseline at month 12,[e] mean (SD)		−51.7 (53.7)	−32.6 (52.9)
sTST, min			
Baseline,[f] mean (SD)	300.0 (89.7)	317.7 (91.1)	315.7 (79.2)
Month 6,[g] mean (SD)	343.6 (78.2)	387.0 (69.6)	362.9 (80.8)
Change from baseline at month 6,[h] LSM (SE)	51.1 (11.6)	70.9 (11.5)	66.1 (12.2)
Treatment difference at month 6,[h] LSM (SE)		19.8 (11.6)	15.0 (11.8)
Month 12,[i] mean (SD)		388.1 (58.5)	370.1 (69.1)
Change from baseline at month 12,[j] mean (SD)		60.7 (62.6)	66.3 (62.2)

[a] PBO, $n = 59$; LEM5, $n = 60$; LEM10, $n = 57$.
[b] PBO, $n = 51$; LEM5, $n = 50$; LEM10, $n = 46$.
[c] PBO, $n = 51$; LEM5, $n = 49$; LEM10, $n = 46$.
[d] LEM5, $n = 47$; LEM10, $n = 43$.
[e] LEM5, $n = 46$; LEM10, $n = 43$.
[f] PBO, $n = 59$; LEM5, $n = 60$; LEM10, $n = 55$.
[g] PBO, $n = 50$; LEM5, $n = 50$; LEM10, $n = 45$.
[h] PBO, $n = 50$; LEM5, $n = 49$; LEM10, $n = 45$.
[i] LEM5, $n = 47$; LEM10, $n = 42$.
[j] LEM5, $n = 46$; LEM10, $n = 42$.
Subjective sleep onset latency (sSOL) values were log-transformed and statistical comparisons made using the least squares geometric mean (LSGM), based on a mixed-effects model of repeated measures (MMRM) evaluating the LSGM treatment ratio between placebo (PBO) and lemborexant (LEM). For other variables, analyses are based on an MMRM evaluating the least squares mean (LSM) treatment difference between PBO and LEM. LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; Q, quartile; sSE, subjective sleep efficiency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset.

vs PBO for the Asian subgroup, consistent with the overall study population (Table 2; Supplementary Fig. S2A). Subjects in the Asian subgroup treated with LEM5 and LEM10 showed greater numerical median decreases in sSOL from baseline vs PBO at each time point in Period 1, beginning as early as week 1; these decreases persisted through Period 2. At month 12, the median change from baseline in sSOL was −25.7 min with LEM5 and −27.1 min with LEM10 (Table 2; Fig. 2A).

The LSM treatment differences for sSE showed greater numerical increases from baseline for both LEM groups vs PBO for the Asian subgroup at month 6 (Table 2; Supplementary Fig. S2B). LSM treatment differences for sSE were larger for LEM5 and LEM10 vs PBO at month 6 for the overall study population (Supplementary Fig. S2B). In the Asian subgroup, LEM5 and LEM10 were associated with greater numerical mean increases in sSE at months 2–6 of Period 1 vs PBO. The improvements in sSE with LEM5 and LEM10 were maintained during Period 2, with mean increases from baseline of 16.1% and 15.3% at month 12, respectively (Table 2; Fig. 2B).

At 6 months, the LSM treatment difference for sWASO showed a greater numerical decrease from baseline for LEM5 vs PBO for the Asian subgroup (Table 2; Supplementary Fig. S2C). The LSM treatment difference for LEM10 vs PBO was small but favored LEM10 for this subgroup. LSM treatment differences for sWASO showed greater reductions from baseline at month 6 with LEM5 and LEM10 vs PBO for the overall study population (Supplementary Fig. S2C). In the Asian subgroup, LEM5 was associated with greater numerical mean decreases vs PBO in sWASO at months 2–6 of Period 1, whereas mean decreases from baseline in sWASO with LEM10 were similar to those seen with PBO for these time points (Fig. 2C). The treatment

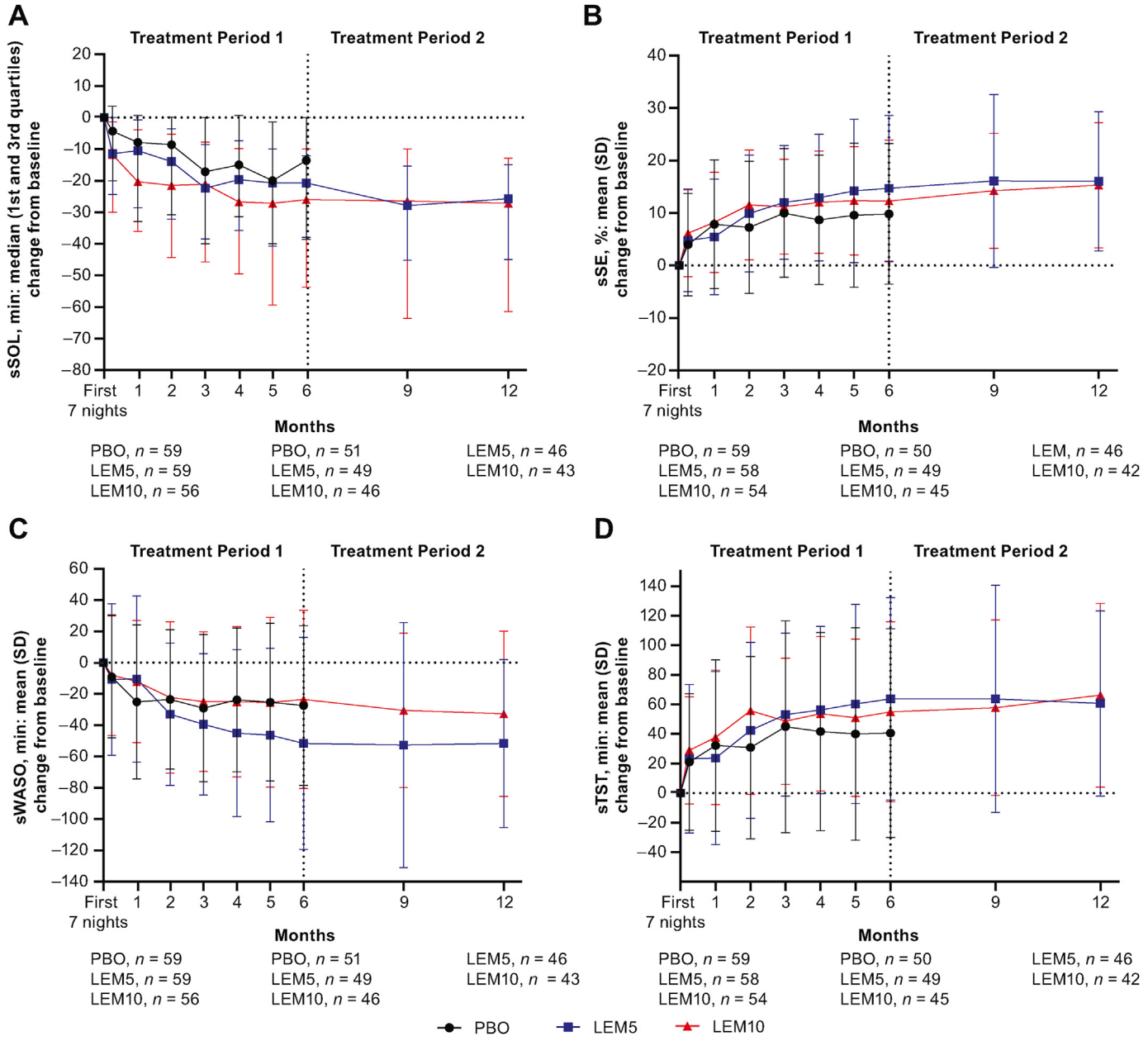

Fig. 2. Change from baseline in subjective sleep parameters over 12 months in the Asian subgroup for (A) subjective sleep onset latency (sSOL), (B) subjective sleep efficiency (sSE), (C) subjective wake after sleep onset (sWASO), and (D) subjective total sleep time (sTST). sSOL values were log transformed. LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; SD, standard deviation.

effect of LEM for sWASO during Period 2 was similar to month 6 in the Asian subgroup, with a mean change of −51.7 min with LEM5 and −32.6 min with LEM10 at month 12 (Table 2; Fig. 2C).

For sTST, the LSM treatment differences showed numerically greater increases from baseline for LEM5 and LEM10 compared with PBO for the Asian subgroup at month 6 (Table 2; Supplementary Fig. S2D). LSM treatment differences for sTST showed greater increases from baseline with LEM5 and LEM10 vs PBO at month 6 for the overall study population (Supplementary Fig. S2D). LEM5 and LEM10 were associated with greater numerical mean increases in sTST for the Asian subgroup at months 2–6 of Period 1 (Fig. 2D). The improvements with LEM seen in these subjects were sustained through Period 2, with mean increases from baseline of 60.7 min with LEM5 and 66.3 min with LEM10 at month 12 (Table 2; Fig. 2D).

3.3. Insomnia Severity Index

Numerically greater decreases from baseline (showing improvement) in ISI total score were observed at months 1, 3, and 6 for LEM5 and LEM10 vs PBO in the Asian subgroup (Fig. 3). Decreases in ISI total score persisted through Period 2 with both LEM doses; mean changes from baseline with LEM5 and LEM10 were −10.6 and −9.9 at month 12, respectively.

3.4. Patient Global Impression–Insomnia version

A greater percentage of Asian subjects receiving LEM5 or LEM10 vs PBO gave a positive response to the PGI-I items "medication helped me sleep" and "medication shortened time to fall asleep" at months 1, 3, and 6 (Fig. 4A and B). At months 9 and 12, >80% of LEM-treated subjects still agreed with the "medication helped me sleep" statement, and >75% agreed that LEM "shortened time to fall asleep."

For the PGI-I item, "increased total sleep time," more Asian subjects receiving LEM5 and LEM10 had a positive response at month 1 compared with subjects receiving PBO (Fig. 4C). More than 65% of LEM-treated subjects gave positive responses at months 9 and 12.

Numerically larger percentages of LEM-vs PBO-treated subjects agreed that the "appropriateness of medication strength" was "just right" at months 1, 3, and 6 (Fig. 4D), and >70% of LEM-treated subjects endorsed this statement at months 9 and 12.

3.5. Safety and tolerability

Overall, TEAEs were generally of mild to moderate severity during both study periods (Table 3). The most common TEAEs were nasopharyngitis and somnolence over the full study (Periods 1 and 2; Table 3 and Supplemental Table S1). For LEM5 and LEM10, the incidence of somnolence was higher during Period 1 than Period 2, decreasing from 9.8% and 10.3% to 0% and 6.1% in the LEM5 and LEM10 groups, respectively. The incidence of nasopharyngitis also decreased in Period 2 (Table 3). Over 12 months, serious AEs occurred in only two subjects receiving LEM5 and no subjects receiving LEM10. During Period 1, four subjects (two in each LEM group) experienced a TEAE leading to study drug withdrawal; during Period 2 there were no withdrawals owing to TEAEs.

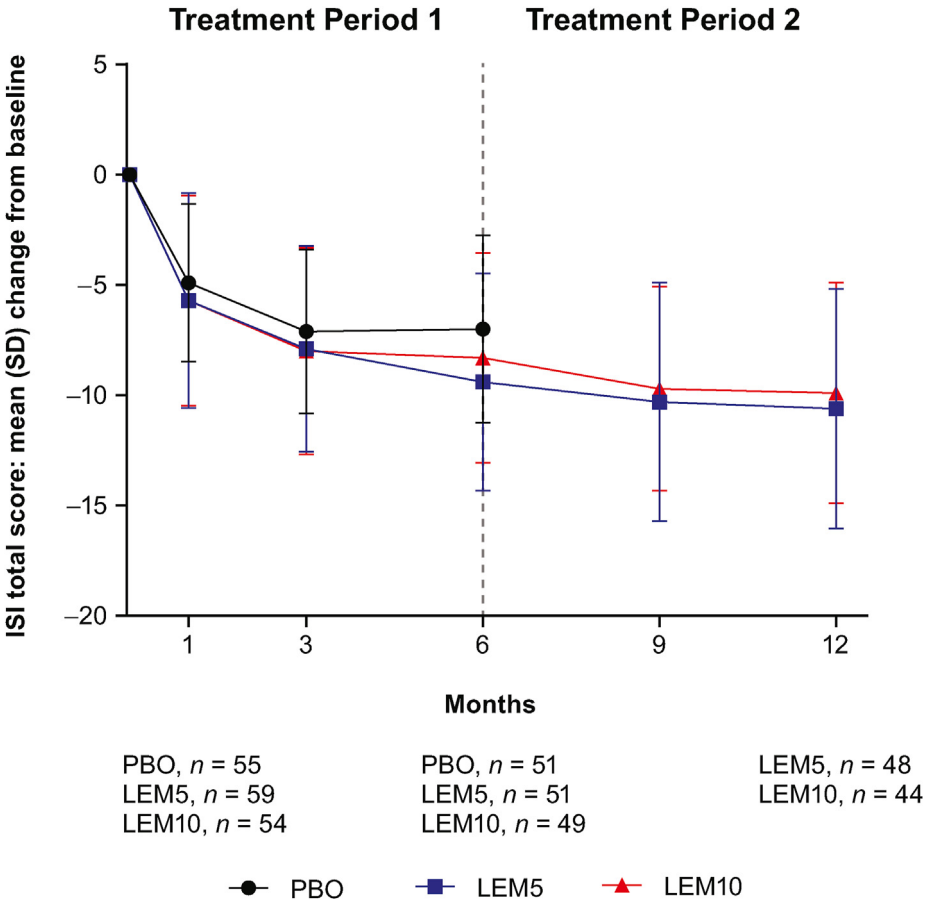

Fig. 3. Change from baseline in total Insomnia Severity Index (ISI) score over 12 months for the Asian subgroup. LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; SD, standard deviation.

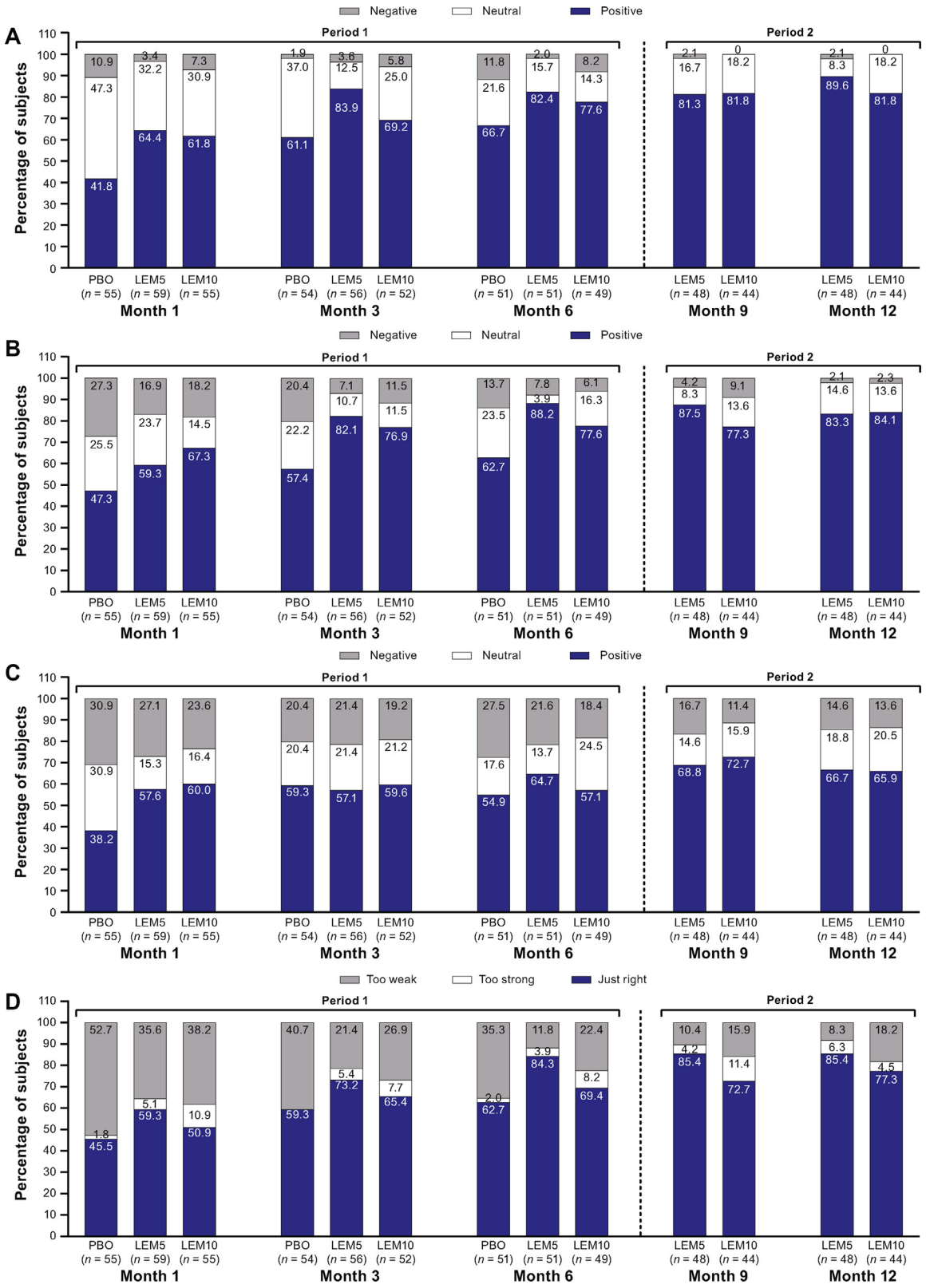

Fig. 4. Percentage of subjects reporting each response for Patient Global Impression–Insomnia scale items (A) "medication helped me sleep," (B) "shortened time to fall asleep," (C) "increased total sleep time," and (D) "appropriateness of medication strength," over 12 months in the Asian subgroup. Percentages are based on the total number of subjects with nonmissing values in the relevant treatment group. LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo.

4. Discussion

In this analysis of 178 Asian subjects enrolled in a large phase 3 trial of LEM for treatment of insomnia disorder, LEM treatment demonstrated efficacy in improving sleep diary-based sleep outcomes vs PBO at 6 months. Importantly, the benefits of LEM treatment were sustained through 12 months, demonstrating the long-term effectiveness of LEM in this population. Both doses of LEM improved sleep parameters, but with some observed differences by dose. LEM10 appeared to be associated with a greater change from baseline in sSOL while LEM5 appeared to be associated with greater change from baseline in sSE, sWASO, and sTST in the subgroup of Asian subjects. These differences are likely attributable to the small number of subjects in each dose group.

These findings were generally consistent with the results observed in the overall population of Study 303, in which LEM-treated subjects experienced greater improvement than PBO-treated subjects in sSOL, sSE, sWASO, and sTST, improvements that were sustained over 12 months [13,15]. As discussed in a previous report about the Japanese subgroup of Study 303 [19], a population PK model of LEM found that race did not have clinically meaningful effects on clearance of LEM, and dose adjustments are not required for LEM based on age and sex [17]. Thus, differences in the efficacy and safety of LEM in the Asian subgroup were not anticipated. The consistency in findings between the Asian subgroup and overall study population supports product labeling that does not recommend dose adjustments based on the patient's ethnicity [23].

In the Asian subgroup, LEM treatment also demonstrated efficacy in reducing subject-perceived severity of insomnia. Subjects treated with LEM5 and LEM10 experienced greater decreases from baseline in ISI total score compared with PBO at 6 months, which persisted through 12 months with both LEM doses. When Asian subjects' perceptions of their medication were measured, subjects receiving LEM were more likely to give positive responses to the four items of the PGI-I scale than those receiving PBO. At 9 and 12 months, >75% of Asian subjects receiving LEM agreed that their medication "helped them sleep" and "shortened time to fall asleep," and >70% reported their medication strength was "just right." These positive perceptions of LEM treatment among Asian subjects reinforce the potential benefits of LEM in this population and suggest that subjects do not develop tolerance to the drug over time.

The safety profile of LEM in the Asian subgroup was consistent with that seen in the overall population and the Japanese subgroup [15,19]. In each of these groups, somnolence and nasopharyngitis were the most commonly reported TEAEs [15,19]. TEAEs were

Table 3
Summary of TEAEs by treatment period for Asian subgroup (over 12 months; Safety Analysis Set).

Period 1	PBO ($n = 59$)	LEM5 ($n = 61$)	LEM10 ($n = 58$)
Category, *n* (%)			
Any TEAE	29 (49.2)	17 (27.9)	27 (46.6)
Any treatment-related TEAE	1 (1.7)	7 (11.5)	8 (13.8)
Any severe TEAE	0	1 (1.6)	0
Any serious TEAE	0	1 (1.6)	0
TEAE leading to study drug withdrawal	0	2 (3.3)	2 (3.4)
TEAEs with incidence >3% in any active treatment group, *n* (%)			
Nasopharyngitis	12 (20.3)	7 (11.5)	11 (19.0)
Somnolence	0	6 (9.8)	6 (10.3)
Headache	1 (1.7)	2 (3.3)	1 (1.7)
Ligament sprain	1 (1.7)	0	2 (3.4)
Sleep paralysis	0	0	2 (3.4)
Period 2		LEM5[a] ($n = 51$)	LEM10[a] ($n = 49$)
Category, *n* (%)			
Any TEAE		15 (29.4)	19 (38.8)
Any treatment-related TEAE		3 (5.9)	4 (8.2)
Any severe TEAE		1 (2.0)	0
Any serious TEAE		1 (2.0)	0
TEAE leading to study drug withdrawal		0	0
TEAEs with incidence >3% in any active treatment group, n (%)			
Nasopharyngitis		2 (3.9)	3 (6.1)
Somnolence		0	3 (6.1)
Influenza		1 (2.0)	3 (6.1)
Sleep paralysis		2 (3.9)	2 (4.1)
Headache		1 (2.0)	2 (4.1)
Cystitis		0	2 (4.1)
Full study period (combined Period 1 and Period 2)		LEM5 ($n = 61$)	LEM10 ($n = 58$)
Category, *n* (%)			
Any TEAE		27 (44.3)	33 (56.9)
Any treatment-related TEAE		9 (14.8)	12 (20.7)
Any severe TEAE		2 (3.3)	0
Any serious TEAE		2 (3.3)	0
TEAE leading to study drug withdrawal		2 (3.3)	2 (3.4)
TEAEs with incidence >4% in any active treatment group, *n* (%)			
Nasopharyngitis		8 (13.1)	14 (24.1)
Somnolence		6 (9.8)	9 (15.5)
Influenza		2 (3.3)	4 (6.9)
Headache		3 (4.9)	2 (3.4)

[a] Only those subjects who had received LEM in both Periods 1 and 2 at the indicated dose were included in this analysis.
Treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. Within each treatment period, subjects with ≥2 AEs with the same preferred term were counted only once for that preferred term.
LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo.

generally mild to moderate in each of these groups (≤5% of TEAEs were severe in any treatment group within each subgroup) [15,19]. Of note, in the overall population [15] and the Asian subgroup, the incidence of somnolence in both LEM groups was lower during Period 2; this was also true of nasopharyngitis. There were no new safety signals with continued LEM treatment beyond 6 months in the overall population [15] or among Asian subjects, suggesting that the frequency of TEAEs may reduce over time with LEM treatment.

There are some limitations to consider in interpreting this subgroup analysis. Subjects were not randomized to treatment based on race, and this analysis was not adequately powered to demonstrate differences between treatment groups. The Asian subgroup of 178 subjects comprised <20% of the overall study population; thus, the small sample size contributed to wide confidence intervals for the estimated treatment differences. The Asian subgroup is also predominantly of Japanese ethnicity, and results from this subgroup do not provide insight into potential differences between Asian ethnic groups. An additional potential limitation of the study is the use of subjective sleep diary data for sleep outcomes rather than objective PSG data. However, results of sleep diary-based outcome measures have been shown to be consistent with PSG-based outcomes in subjects with insomnia [12,13].

5. Conclusions

In conclusion, this analysis provides evidence that LEM is effective in improving subjective sleep parameters and is well tolerated in Asian subjects with insomnia disorder who received LEM treatment for up to 12 months. In addition, Asian subjects had positive perceptions of LEM effects on insomnia severity, medication effectiveness, and drug strength that were sustained for 1 year. These findings provide further guidance for the use of LEM in the Asian population in real-life settings and the personalization of treatment decisions.

Author contributions

AD, YI, KH, and NK were involved in the interpretation of the data. KP was involved in the statistical analysis. SCL and CHY were investigators and were involved in the data collection and interpretation of the data. THL and CLH were investigators and were involved in the data collection. JY and MM were involved in the study design. KP and MM were involved in the study design and data analyses. All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript.

Data availability

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

Financial disclosure: AD is an employee of Eisai Singapore Pte Ltd. KP and JY are employees of Eisai Ltd. YI has received grants and/or personal fees from Eisai Inc., Eisai Ltd., Merck Sharp & Dohme, and Takeda in relation to the submitted work; has received grants or personal fees from Alfresa Pharma, Philips, and Koike Medical; and has received funding for clinical trials from Astellas and Janssen outside of the submitted work. KH has received grants/personal fees and consultant/speaker fees from Eisai Inc.; has received funding for clinical trials from Eisai Inc.; and has received personal fees from and Eisai Ltd., and Merck Sharp & Dohme. SCL has received grants/personal fees from Eisai Inc. CHY has no conflict of interests relevant to this study. THL and CLH have received funding for clinical trials from Eisai Inc. and have no conflicts of interests relevant to this study. NK is an employee of Eisai Co., Ltd. MM is an employee of Eisai Inc.; she has been issued a patent and has pending and planned patents broadly related to this work.

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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.sleepx.2022.100044.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleepx.2022.100044.

References

[1] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
[2] Kawada T, Yosiaki S, Yasuo K, et al. Population study on the prevalence of insomnia and insomnia-related factors among Japanese women. Sleep Med 2003;4(6):563–7.
[3] Itani O, Kaneita Y, Munezawa T, et al. Nationwide epidemiological study of insomnia in Japan. Sleep Med 2016;25:130–8.
[4] Cao XL, Wang SB, Zhong BL, et al. The prevalence of insomnia in the general population in China: a meta-analysis. PLoS One 2017;12(2):e0170772.
[5] Li N, Xu G, Chen G, et al. Sleep quality among Chinese elderly people: a population-based study. Arch Gerontol Geriatr 2020;87:103968.
[6] Zhang YS, Jin Y, Rao WW, et al. Prevalence and socio-demographic correlates of poor sleep quality among older adults in Hebei province, China. Sci Rep 2020;10(1):12266.
[7] Chung S, Cho SW, Jo MW, et al. The prevalence and incidence of insomnia in Korea during 2005 to 2013. Psychiatry Investig 2020;17(6):533–40.
[8] Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res 2017;26(6):675–700.
[9] Lie JD, Tu KN, Shen DD, et al. Pharmacological treatment of insomnia. P T 2015;40(11):759–71.
[10] Beuckmann CT, Ueno T, Nakagawa M, et al. Preclinical in vivo characterization of lemborexant (E2006), a novel dual orexin receptor antagonist for sleep/wake regulation. Sleep 2019;42(6):zsz076.
[11] Moline M, Zammit G, Yardley J, et al. Lack of residual morning effects of lemborexant treatment for insomnia: summary of findings across 9 clinical trials. Postgrad Med 2021;133(1):71–81.
[12] Murphy P, Moline M, Mayleben D, et al. Lemborexant, a dual orexin receptor antagonist (DORA) for the treatment of insomnia disorder: results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. J Clin Sleep Med 2017;13(11):1289–99.
[13] Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep 2020;43(9):zsaa123.
[14] Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. JAMA Netw Open 2019;2(12):e1918254.

[15] Yardley J, Kärppä M, Inoue Y, et al. Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial. Sleep Med 2021;80:333–42.
[16] Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. J Natl Med Assoc 2002;94(10 Suppl):1–26.
[17] Lalovic B, Majid O, Aluri J, et al. Population pharmacokinetics and exposure-response analyses for the most frequent adverse events following treatment with lemborexant, an orexin receptor antagonist, in subjects with insomnia disorder. J Clin Pharmacol 2020;60(12):1642–54.
[18] Landry I, Nakai K, Ferry J, et al. Pharmacokinetics, pharmacodynamics, and safety of the dual orexin receptor antagonist lemborexant: findings from single-dose and multiple-ascending-dose phase 1 studies in healthy adults. Clin Pharmacol Drug Dev 2021;10(2):153–65.
[19] Inoue Y, Watanabe T, Takashima S, et al. Efficacy and safety of lemborexant in adults with insomnia: comparing Japanese and non-Japanese subgroups from the global, phase 3, randomized, double-blind, placebo-controlled SUNRISE 2 study. J Clin Sleep Med 2021;17(5):1067–74.
[20] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
[21] Roth T, Soubrane C, Titeux L, et al., Zoladult Study Group. Efficacy and safety of zolpidem-MR: a double-blind, placebo-controlled study in adults with primary insomnia. Sleep Med 2006;7(5):397–406.
[22] Walsh JK, Soubrane C, Roth T. Efficacy and safety of zolpidem extended release in elderly primary insomnia patients. Am J Geriatr Psychiatry 2008;16(1):44–57.
[23] Eisai Inc. Prescribing information for DAYVIGO™ (lemborexant) tablets. 2021.