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ORIGINAL RESEARCH

Efficacy of Lemborexant in Adults ≥ 65 Years of Age with Insomnia Disorder

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ABSTRACT

Background: Pharmacologic treatments are available to treat insomnia, a common and burdensome sleep disorder, but may be contraindicated in older adults who are prone to side effects from sleep-promoting drugs. These analyses of sleep diary data from Study E2006-G000-303 (Study 303) investigated the benefits of lemborexant 5 mg (LEM5) and 10 mg (LEM10) in the subgroup age ≥ 65 years with insomnia.

Method: Study 303, a 12-month, double-blind study of LEM5 and LEM10 in adults (age ≥ 18 years) with insomnia disorder (sleep onset and/or maintenance difficulties) assessed subject-reported (subjective) sleep-onset latency (sSOL), sleep efficiency (sSE), wake after sleep onset (sWASO), and total sleep time (sTST). Morning sleepiness/alertness, insomnia severity (Insomnia Severity Index [ISI]), fatigue (Fatigue Severity Scale [FSS]), perceptions of sleep-related medication effects (Patient Global

Prior Presentations This manuscript is based on work that has been previously presented. (1) Moline M, et al. Long-term efficacy and safety of lemborexant in elderly adults with insomnia disorder: results from SUNRISE-2 (E2006-G000-303). Presented at SLEEP 2020, August 27–30, 2020, virtual meeting. (2) Yardley J, et al. Impact of lemborexant on insomnia disease severity and fatigue in elderly subjects with insomnia. 3925. Presented at the American Academy of Family Physicians 2020 Family Medicine Experience Virtual Conference, October 13–17, 2020, virtual meeting. (3) Drake C, et al. Subject-reported perception of long-term effectiveness of lemborexant versus placebo in nonelderly and elderly subgroups. 3927. Presented at the American Academy of Family Physicians 2020 Family Medicine Experience Virtual Conference, October 13–17, 2020, virtual meeting. (4) Moline M, et al. Long-term efficacy and safety of lemborexant in elderly adults with insomnia disorder. 3928. Presented at the American Academy of Family Physicians 2020 Family Medicine Experience Virtual Conference, October 13–17, 2020, virtual meeting.

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Impression–Insomnia [PGI-I] questionnaire), and safety were also evaluated.

Results: In this subgroup of older adults (≥ 65 years; $n = 262$), there were significantly larger changes from baseline for sSOL, sSE, sTST, and sWASO with LEM5 and LEM10 versus placebo through month 6 (except sWASO month 1), indicating improvement; these improvements were sustained through month 12. Subject-reported increases in morning alertness were significantly greater with one or both LEM doses versus placebo through month 6 and sustained through month 12. There were significantly larger ISI total and daytime functioning score decreases (improvement) from baseline with LEM versus placebo at months 1, 3, and 6 (total score: both doses; daytime functioning: LEM5 month 1 and both doses months 3 and 6) and decreases from baseline FSS at months 1 and 3 (LEM5) and month 6 (both doses), sustained to month 12. Compared with placebo, more subjects reported that LEM (both doses) positively impacted ability to sleep, time to fall asleep, and TST through month 6, sustained to month 12, with no rebound after drug withdrawal. LEM was well tolerated to month 12; mild somnolence was the most common treatment-emergent adverse event.

Conclusions: Improvements in subject-reported efficacy in LEM-treated adults age ≥ 65 years with insomnia were observed as early as the first week of treatment and sustained through end of month 12. LEM was well tolerated.

Clinical trials registration: ClinicalTrials.gov identifier NCT02952820: E2006-G000-303; Study 303; SUNRISE-2 (First posted: October 2016); EudraCT 2015-001463-39 (First posted: November 2016).

PLAIN LANGUAGE SUMMARY

Insomnia is a common sleep disorder associated with significant difficulties, particularly in older adults. Although there are many drug treatments available, some are associated with the important risk of side effects and may not adequately treat sleep maintenance (ability to stay asleep), which is a frequent sleep complaint in older people. Lemborexant has been approved in multiple countries for the treatment of adults with insomnia based on studies that show lemborexant improved adults' ability to fall asleep and stay asleep and is well tolerated. To examine the long-term benefit of lemborexant, we investigated subject-reported benefits and safety of lemborexant in older (≥ 65 years) adults who participated in a 1-year study. The results showed that within the first few days of taking lemborexant, and lasting through 12 months of treatment, nightly lemborexant improved nighttime sleep (that is, it reduced the time it took to fall asleep, reduced the time awake during the night, and increased total sleep time) more than placebo. Morning alertness improved more in older adults who took lemborexant compared with placebo. In addition, those who took lemborexant also reported that their insomnia symptoms were less severe and they had less fatigue compared with placebo. Lemborexant was well tolerated in older adults. These results suggest that lemborexant may be a good option for older adults with insomnia disorder.

Keywords: Insomnia; Lemborexant; Orexin receptor antagonists; Sleep; Elderly

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Key Summary Points

Why carry out the study?
To study the efficacy and safety of lemborexant 5 mg (LEM5) and 10 mg (LEM10) in a subgroup of patients age ≥ 65 years with insomnia
W*hat was learned from this study?*
LEM5 and LEM10 decreased subject-reported time to fall asleep and time awake after falling asleep and increased total sleep time within the first few days of treatment, findings that were sustained through 12 months of nightly treatment in adults age ≥ 65 years with insomnia disorder
LEM5 and LEM10 reduced insomnia severity and fatigue more than placebo
The change from baseline in alertness was larger for subjects treated with LEM (both doses) compared with placebo
LEM5 and LEM10 were well tolerated in adults age ≥ 65 years with insomnia disorder

INTRODUCTION

Chronic insomnia affects up to 50% of adults ≥ 60 years of age, influencing quality of life, daytime functioning, and mental health [1, 2]. Older adults may experience sleep-related changes, including early awakenings and difficulty maintaining sleep [1]. A bidirectional relationship in older patients likely exists between sleep disturbances and comorbidities, including depression, heart failure, chronic respiratory disorders, pain, gastro-esophageal reflux disease, and dementia [3]. In addition, medications used to treat comorbidities may also negatively impact sleep [3].

Several challenges exist with available therapies used to treat older adults with chronic insomnia. For example, cognitive-behavioral therapy for insomnia is a first-line insomnia treatment that has been studied in older adults [4, 5]. However, when this is not effective or available, use of pharmacotherapy should be considered [5, 6]. Sedative-hypnotic benzodiazepine and non-benzodiazepine (Z-drug) receptor agonists such as zolpidem are prescribed frequently to treat insomnia in adults [2, 7–11]. However, not all of these medications may be effective or indicated to treat sleep maintenance insomnia, which are among the most common sleep complaints in older adults [12]. Adverse effects from these medications are frequently reported in older adults, including excessive sleepiness, poor motor coordination, falls, hip fractures, and risk of unintentional injury [2, 11, 13]. Other serious risks of prolonged use of benzodiazepine and Z-drug hypnotics include tolerance, dependence, withdrawal symptoms, and rebound insomnia [1, 11]. Therefore, sedative-hypnotics are on the Beers list of potentially inappropriate medications in older adults [14]. Antidepressants, including doxepin and trazodone, are used to treat insomnia due to their sedative effects [8]. Low-dose doxepin, a tricyclic antidepressant, is approved for the treatment of insomnia characterized by difficulties with sleep maintenance [8, 11]. Trazodone is also prescribed off-label for insomnia; however, it is not approved as a sleep aid, and common adverse events include somnolence/sedation, dizziness, constipation, and blurred vision [15]. There is insufficient evidence that trazodone is efficacious in chronic insomnia, especially in older adults, and it is not recommended by the American Academy of Sleep Medicine [6, 11]. Thus, there is an unmet need for sleep medicines with a favorable risk–benefit ratio in older patients.

Dual orexin receptor antagonists (DORAs) provide an alternative to older treatments for insomnia. DORAs target the orexin signaling pathway, which is involved in sleep/wake regulation [16]. Thus, DORAs have the potential to effectively treat insomnia with fewer next-day residual effects than sleep-promoting drugs with different mechanisms of action, such as benzodiazepines and Z-drugs [16–18]. Lemborexant (LEM) is a competitive DORA antagonist approved in multiple countries, including the USA, Canada, Australia, Japan, and several other Asian countries for the treatment of insomnia disorder in adults.

Study E2006-G000-303 (Study 303; SUNRISE-2) was a pivotal phase 3 study demonstrating that LEM 5 mg (LEM5) and 10 mg (LEM10) improved sleep with the initial doses, and these

benefits were sustained through the 12-month study endpoint [19, 20]. Furthermore, LEM was well tolerated, and treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity.

To investigate long-term LEM efficacy and safety specifically in subjects ≥ 65 years of age with insomnia, we conducted a post hoc analysis of Study 303. Analyses included subject-reported sleep diary data and other subject-reported assessments, including the Insomnia Severity Index (ISI), Fatigue Severity Scale (FSS), and Patient Global Impression-Insomnia (PGI-I) questionnaires. Rebound and safety data from this subpopulation are also reported.

METHODS

Study 303 [19], a 12-month phase 3, global, multicenter, randomized, double-blind, parallel-group study, was conducted in subjects with insomnia disorder who met the criteria as described in the *Diagnostic and Statistical Manual of Mental Disorder*, Fifth Edition [21]. In brief, these criteria were adults (both males and females ≥ 18 years of age) with a history of subjective sleep onset latency (sSOL) ≥ 30 min and/or subjective wake after sleep onset (sWASO) ≥ 60 min at least 3 nights/week in the prior 4 weeks (confirmed by sleep diary), regular time in bed (i.e., 7–10 h), and ISI score ≥ 15 [19]. The first 6 months of the study were placebo controlled, after which subjects in the placebo group were rerandomized to receive LEM5 or LEM10 for an additional 6 months (not reported); those subjects initially randomized to LEM continued treatment with their assigned dose.

Subjects were ineligible if they were diagnosed with a sleep disorder (e.g., moderate-to-severe sleep apnea, periodic limb movement disorder [PLMD], restless legs syndrome, circadian rhythm sleep disorder, narcolepsy, and certain parasomnias). Additional exclusion criteria included subjects with an Apnea–Hypopnea Index score > 15 or PLMD score > 15 in adults (≥ 65 years of age) who underwent diagnostic polysomnography within 1 year prior to consent, STOP-Bang score ≥ 5, International Restless Legs Scale score ≥ 16, and Epworth Sleepiness Scale score > 15. Full exclusion criteria have been previously published [19].

The protocol, protocol amendments or revisions, and informed consent form were approved by a qualified institutional review board and/or independent ethics committee. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. All subjects completed written informed consent before study participation, including consent to publish and anonymity. The study is registered on ClinicalTrials.gov (NCT02952820) and on EudraCT (2015–001463-39). Additional study details, including site information, can be found at https://clinicaltrials.gov/study/NCT02952820.

Treatment

Following a placebo run-in period of approximately 2 weeks, subjects were randomized (1:1:1) to receive placebo, LEM5, or LEM10 for the first 6-month period (Treatment Period 1) [19]. Subjects in the two LEM groups continued their initially assigned dose to Month 12 for the second 6-month period (Treatment Period 2). Subjects who initially received placebo were rerandomized to LEM5 or LEM10 at Month 6. At the end of Treatment Period 2 (12 months), the study drug was stopped abruptly, and there was an approximately 2-week follow-up without treatment.

Efficacy Outcomes

Subject-reported (i.e., subjective) sleep parameters were assessed with data from electronic sleep diaries, which were completed every day within 1 h of morning awakening. Endpoints included sSOL (subject's estimated time [min] from the time they attempted to fall asleep until sleep onset), subjective sleep efficiency (sSE; total time spent asleep divided by time in bed, calculated using sleep diary entries), sWASO (subject-estimated sum of time [min] of wake during night after initial sleep onset), and subject-estimated (subjective) total sleep time (sTST; derived minutes of sleep from sleep onset until the time they stopped trying to sleep for the night). Subjective sleep onset and sleep maintenance endpoints were analyzed during the placebo run-in for

1 week at baseline, at nights 1–7, and at the last nights of months 1–6, 9, and 12.

Subjects reported morning sleepiness/alertness using sleep diaries in response to the question, "How sleepy/alert do you feel this morning?" Scores ranged from 1–9, with 1 indicating extremely sleepy and 9 indicating extremely alert. Morning sleepiness/alertness was analyzed at several timepoints: for the week at baseline; after the first 7 days following dose 1 in treatment period 1; after the final 7 days before the study visit at months 1–6; and after the last 7 days of months 9 and 12 in treatment period 2.

The ISI, a validated seven-item self-report questionnaire [22], was used by subjects to rate their insomnia severity. Each item of the ISI is assessed on a 5-point Likert scale (0–5, with 0 indicating no problem and 4 indicating very severe problem), yielding a maximum score of 28. Higher scores on the ISI indicate worse insomnia; ISI scores were assessed at baseline and the end of months 1, 3, 6, 9, and 12. The ISI daytime functioning score (corresponding to items 4–7) and the total score were analyzed separately. The percentage of subjects with a decrease from baseline in the ISI total score of at least 7 points following each timepoint was calculated for the ISI responder analysis. The percentage of subjects who achieved remission from insomnia (defined as ISI total score < 10 or < 8) at each timepoint was calculated for the ISI remitter analysis. These thresholds for change are proposed to be clinically meaningful [23, 24]. An ISI reduction of 8 points was optimal to identify participants with marked improvement, whereas a cutoff of 10 was optimal for detecting insomnia in a community sample [24].

The self-reported FSS questionnaire was used to assess the impact of fatigue [25]. Each of the nine items in the questionnaire is rated on a 7-point scale (1–7, with 1 indicating strongly disagree and 7 indicating strongly agree), yielding a maximum score of 63. Higher scores indicate worse fatigue. The FSS was assessed at baseline and the end of months 1, 3, 6, 9, and 12.

Patients' perceptions of the effects of medication on their sleep during or at the end of treatment relative to their sleep prior to the initiation of study treatment was evaluated with the PGI-I, a self-reported five-item questionnaire [26, 27]. 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, with 1 indicating a positive medication effect, 2 indicating a neutral medication effect, and 3 indicating a negative medication effect. Original item 4 (better sleep) was not assessed herein. Item 4 of this study assessed perceived appropriateness of study medication strength and was measured on a different 3-point scale, with 1 indicating too strong, 2 indicating just right, and 3 indicating too weak. PGI-I was assessed at the end of months 1, 3, 6, 9, and 12.

Rebound insomnia was assessed by analyzing sWASO and sSOL during the follow-up period. The percentage of subjects with sWASO or sSOL more than 5 min longer than during screening was determined at the first, second, and third nights, the average of the first 3 nights, the average of the first 7 nights, and the average of the final 7 nights [20].

Safety Outcomes

Safety outcomes, including clinical laboratory evaluations, vital signs, weight, electrocardiograms, and physical examinations, were assessed at each clinic visit. TEAEs were recorded throughout the study, and severity and relationship to treatment were assessed.

Statistical Analyses

The Full Analysis Set (FAS) included randomized subjects who received ≥ one dose of study drug and had ≥ 1 post-dose primary efficacy measurement. The Safety Analysis Set (SAS) included randomized subjects who received ≥ 1 dose of study drug and had ≥ 1 post-dose safety assessment.

P-values for sleep measures were based on the least squares mean (LSM) treatment differences (active – placebo) using a mixed effect model repeated measure (MMRM) analysis with region, treatment, visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate. The LSM change from baseline (CFB) in subjective sleep parameters was calculated (averaged) over the first 7 nights and for the last 7 days of months 1–6, 9, and 12. Missing values were not imputed. Due to the non-normal distribution of sSOL data, values

were log-transformed, and statistical comparisons were performed using least squares geometric mean treatment ratios (active:placebo).

Similar to the subjective sleep measures, *P*-values for morning sleepiness were based on LSM treatment differences using an MMRM model. LSM treatment differences were calculated (averaged) at the first 7 days and for the last 7 days of months 1, 2, 3, 4, 5, and 6. Missing values were not imputed and assumed to be missing at random (MAR). *P*-values for ISI and FSS total score (FSS-TS) [25] were based on LSM treatment differences using an MMRM model similar to that used for subjective sleep measures and were calculated at the ends of months 1, 3, and 6; missing values were not imputed and assumed to be MAR.

For subjective sleep measures, morning sleepiness, ISI, and FSS, only subjects initially randomized to LEM5 or LEM10 were included in the analyses for after month 6 (treatment period 2), and subjects in the placebo group who were rerandomized to LEM at the start of treatment period 2 were excluded.

For the responder/remitter analysis, nonresponders included subjects who ended the study early. At each timepoint, two-sided 95% confidence intervals were calculated based on normal approximation; *P*-values for between-group comparisons were based on the Cochrane-Mantel–Haenszel test stratified by region [23].

The number and percentage of subjects with a positive medication effect rating on each PGI-I item were analyzed separately. *P*-values were based on a Chi-square test comparison of the number of positive responses or on the strength of the treatment question "just right," with the number of neutral or negative responses combined.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) or other validated software.

RESULTS

Baseline Characteristics

Overall, 262 of 949 (27.6%) subjects in the Study 303 FAS were ≥ 65 years of age (Table 1; Electronic Supplementary Material [ESM] Fig. S1) [19]. In treatment period 2, 138 of 477 (28.9%) LEM-treated adults were ≥ 65 years of age [20]. The median age was 70 (range 65–88) years (Table 1). Baseline demographics were similar across treatment groups (Table 1). Most subjects were female and White.

Subjective Sleep Parameters

Subjects ≥ 65 years of age reported improved sleep parameters. There were significantly larger changes from baseline over the first 7 nights and for the 7 days at the end of each month through month 6 for sleep onset as measured by sSOL in both LEM dose groups compared with placebo (Fig. 1a). Similarly, in both LEM groups, there were significantly larger changes from baseline through the last 7 days of month 6 compared with placebo for sleep maintenance as measured by sSE (Fig. 1b), sWASO (except for month 1; Fig. 1c), and for sTST (Fig. 1d). Improvements seen to month 6 in LEM-treated subjects persisted to month 12 (i.e., treatment period 2) (Fig. 1a–d). Based on sSOL and sWASO measures, there was no clear evidence of rebound insomnia during the 2-week follow-up period after 12 months of LEM5 or LEM10 treatment (ESM Table S1).

Morning Sleepiness/Alertness

Baseline morning sleepiness/alertness scores were similar across groups (Table 1). Compared with placebo, the CFB in morning sleepiness/alertness was significantly greater in the LEM groups over the first 7 days (both doses) and last 7 days of month 1 (LEM5), month 2 (LEM5), and months 3–6 (both doses; Table 2). The improvements experienced by LEM-treated subjects at month 6 (CFB mean [SD], LEM5: 1.0 [1.3]; LEM10: 1.0 [1.3]) persisted to months 9 (CFB mean [SD], LEM5: 1.2 [1.4]; LEM10: 1.0 [1.3]) and 12 (CFB mean [SD], LEM5: 1.4 [1.4]; LEM10: 1.2 [1.5]; treatment period 2).

Table 1 Baseline demographics and characteristics of adults ≥ 65 years of age

Baseline demographics and characteristics	PBO (*n* = 89)	LEM5 (*n* = 87)	LEM10 (*n* = 86)
Age, years			
Mean (SD)	71.0 (4.4)	70.4 (3.9)	71.2 (5.3)
Median (range)	70 (65, 83)	70 (65, 85)	70 (65, 88)
Sex, n (%)			
Male	21 (23.6)	26 (29.9)	25 (29.1)
Female	68 (76.4)	61 (70.1)	61 (70.9)
Race, n (%)			
White	71 (79.8)	72 (82.8)	70 (81.4)
Black or African American	3 (3.4)	0	3 (3.5)
Asian	14 (15.7)	15 (17.2)	13 (15.1)
Other	1 (1.1)	0	0
BMI, mean (SD), kg/m²	26.5 (4.3)	27.5 (5.4)	26.7 (4.3)
Subjective sleep variables, mean (SD)			
sSOL, median (Q1, Q3), min[a]	53.6 (34.6, 80.4)	52.7 (30.7, 82.1)	58.2 (29.3, 84.3)
sSE, mean (SD), %[b]	61.6 (18.3)	63.6 (17.3)	61.0 (15.9)
sWASO, mean (SD), min[c]	140.2 (87.3)	131.4 (77.3)	154.8 (87.2)
sTST, mean (SD), min[b]	312.8 (97.0)	321.1 (91.3)	304.7 (82.5)
Morning sleepiness/alertness score, mean (SD)[a]	4.4 (1.3)	4.4 (1.2)	4.3 (1.3)
ISI total score, mean (SD)[d]	19.1 (3.0)	19.4 (3.2)	19.2 (3.3)
FSS total score, mean (SD)[d]	33.2 (12.7)	35.5 (13.3)	34.9 (13.6)

[a] *n* = 88 (PBO), 86 (LEM5), 86 (LEM10)

[b] *n* = 85 (PBO), 83 (LEM5), 81 (LEM10)

[c] *n* = 87 (PBO), 85 (LEM5), 86 (LEM10)

[d] *n* = 89 (PBO), 87 (LEM5), 86 (LEM10)

BMI body mass index, *FSS* Fatigue Severity Scale, *ISI* Insomnia Severity Index, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *PBO* placebo, *Q* quartile, *SD* standard deviation, *sSOL* subjective sleep-onset latency, *sSE* subjective sleep efficiency, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset

Insomnia Severity

Lemborexant (both doses) significantly reduced subject-reported overall disease severity as measured by the ISI total score compared with placebo, as assessed after 1 month of treatment, which was sustained through 12 months (Fig. 2a). Results for the ISI daytime functioning score were similar to the total score except for month 1 where only the LEM5 versus placebo comparison was statistically significant (Fig. 2b). Although not always statistically

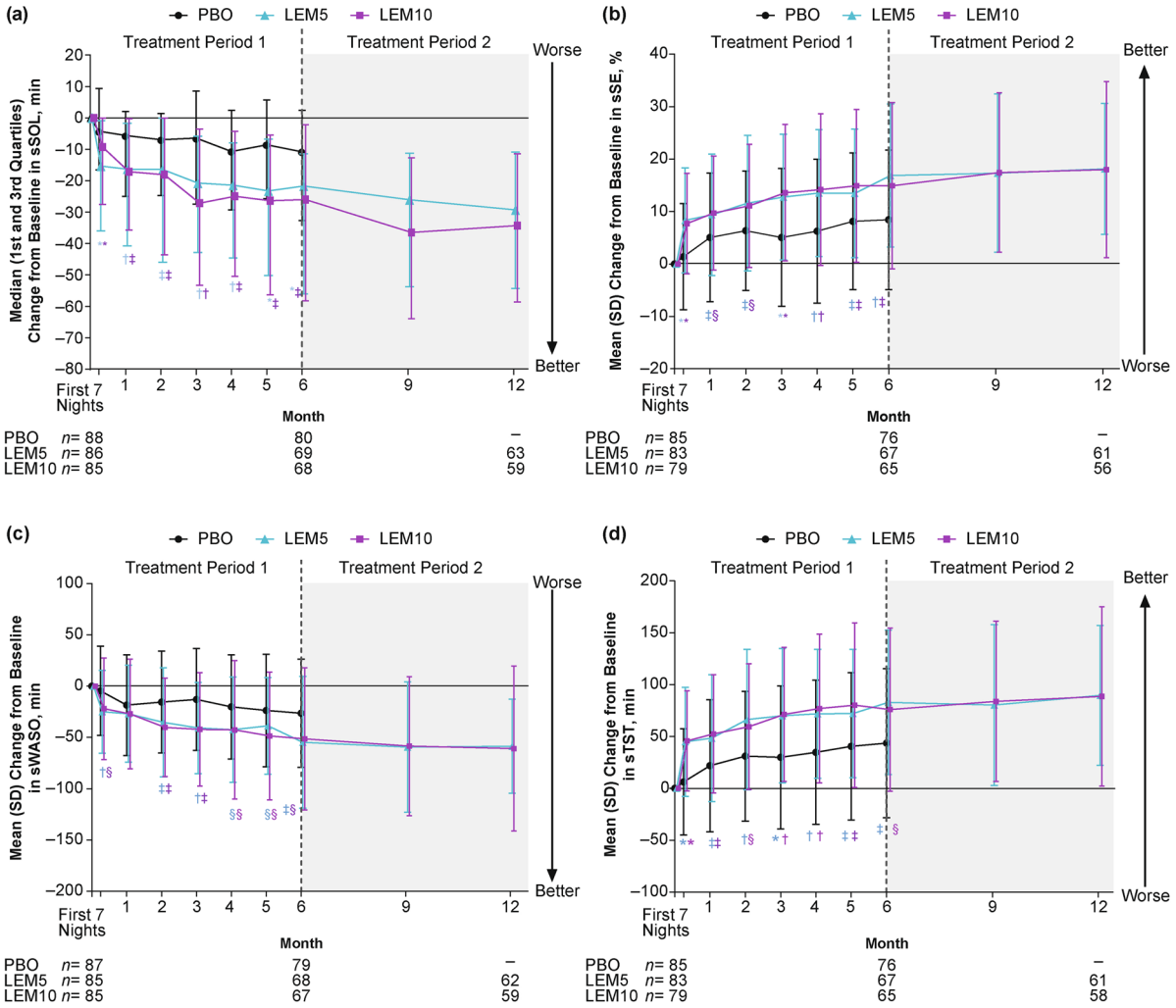


Fig. 1 Change from BL in subject-reported measures of sleep over the first 7 nights through month 12 in subjects ≥ 65 years of age in Study 303. **a–d** Subject-reported measures of sleep onset (sSOL) (**a**), sleep maintenance (sSE, sWASO) (**b**, **c**), and total sleep time (**d**). sSOL values were log-transformed; *P*-values are based on the MMRM analysis evaluating the LSGM treatment ratio between placebo and LEM (**a**). *P*-values for sSE (**b**), sWASO (**c**), and sTST (**d**) are based on the MMRM analysis evaluating the least squares mean treatment difference between placebo and LEM. For the data on or after month 9, the analysis includes only the subjects initially randomized to LEM5 or LEM10. Significant differences are indicated by the asterisk (*$P < 0.0001$ vs. PBO), dagger ($^{\dagger}P < 0.001$ vs. PBO); double dagger ($^{\ddagger}P < 0.01$ vs. PBO); and section sign ($^{\S}P < 0.05$ vs. PBO). *BL* Baseline, *LEM* lemborexant, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LSGM* least squares geometric mean, *MMRM* mixed effect model repeated measure, *PBO* placebo, *sSE* subjective sleep efficiency, *sSOL* subjective sleep onset latency, *sTST* subjective total sleep time, *sWASO* subjective wake after sleep onset

significant, the percentage of ISI responders and remitters was numerically higher in the LEM treatment groups compared with placebo at all timepoints through month 6 and was maintained through month 12 (Table 3).

Fatigue Severity

Mean FSS total scores for the subgroup were previously reported [28]. In summary, CFB on the FSS was significantly decreased (less fatigue) with

Table 2 Morning sleepiness/alertness in adults ≥ 65 years of age during treatment period 1

Morning sleepiness/alertness measures	PBO	LEM5	LEM10
Baseline			
n	88	86	86
Mean (SD)	4.4 (1.3)	4.4 (1.2)	4.3 (1.3)
Median (range)	4.1 (1.1, 7.7)	4.3 (2.1, 7.3)	4.2 (1.0, 7.4)
First 7 days			
n	89	87	85
Mean (SD)	4.3 (1.4)	4.8 (1.2)	4.6 (1.4)
LSM (SE) change from baseline	− 0.1 (0.1)	0.4 (0.1)	0.2 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.5 (0.3, 0.8)*	0.4 (0.1, 0.6)†
Month 1			
n	88	82	79
Mean (SD)	4.6 (1.4)	4.9 (1.2)	4.6 (1.4)
LSM (SE) change from baseline	0.2 (0.1)	0.5 (0.1)	0.3 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.4 (0.1, 0.7)†	0.1 (− 0.2, 0.4)
Month 2			
n	83	80	72
Mean (SD)	4.6 (1.5)	5.1 (1.5)	4.8 (1.5)
LSM (SE) change from baseline	0.2 (0.1)	0.7 (0.1)	0.5 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.5 (0.2, 0.9)†	0.3 (− 0.05, 0.7)
Month 3			
n	80	76	73
Mean (SD)	4.6 (1.5)	5.2 (1.4)	5.1 (1.6)
LSM (SE) change from baseline	0.2 (0.1)	0.7 (0.1)	0.7 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.5 (0.1, 0.9)†	0.5 (0.1, 0.9)†
Month 4			
N	82	73	70
Mean (SD)	4.8 (1.4)	5.2 (1.4)	5.3 (1.6)
LSM (SE) change from baseline	0.3 (0.1)	0.7 (0.1)	0.9 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.4 (0.07, 0.8)§	0.6 (0.2, 0.9)†

Table 2 continued

Morning sleepiness/alertness measures	PBO	LEM5	LEM10
Month 5			
N	80	69	70
Mean (SD)	4.8 (1.5)	5.2 (1.4)	5.1 (1.6)
LSM (SE) change from baseline	0.3 (0.1)	0.8 (0.1)	0.7 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.5 (0.1, 0.9)[†]	0.4 (0.04, 0.8)[§]
Month 6			
n	81	70	68
Mean (SD)	4.8 (1.5)	5.3 (1.5)	5.2 (1.5)
LSM (SE) change from baseline	0.3 (0.1)	0.9 (0.1)	0.9 (0.1)
LSM treatment difference vs. PBO (95% CI)		0.5 (0.2, 0.9)[†]	0.5 (0.1, 0.9)[†]

P values were based on LSM treatment differences using a mixed effect model repeated measure (MMRM) model. Missing values were not imputed and assumed to be missing at random

CI Confidence interval, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LSM* least squares mean, *PBO* placebo, *SD* standard deviation, *SE* standard error

*$P < 0.0001$ vs. placebo; †$P < 0.01$ vs. placebo; §$P < 0.05$ vs placebo

LEM5 versus placebo as assessed at 1 month and 3 months, and for both doses at 6 months of treatment. Improvement in fatigue was sustained through month 12 in LEM-treated subjects (Fig. 2C).

Subject Perceptions of LEM Based on PGI-I

Patient Global Impression–Insomnia scores were evaluated through to 12 months. Subjects treated with LEM reported their study medication had a positive impact on helping them to sleep, reducing time to fall asleep, and TST, versus those who received placebo, as assessed starting at 1 month, continuing to 6 months (Fig. 3a–c). The proportion of subjects who perceived a positive impact of LEM treatment (both doses) was stable from treatment periods 1 to 2.

A significantly greater proportion of subjects in the LEM5 and LEM10 groups indicated the study medication strength was "just right" at 1, 3, and 6 months compared with placebo (Fig. 3d). At both 9 and 12 months, the majority (>60%) of subjects in the LEM5 and LEM10 groups also responded that treatment strength was "just right"; at 12 months, the percentages were higher than reported at 1, 3, and 6 months (Fig. 3d). The proportion of LEM-treated subjects who reported the medication strength as "too weak" did not increase over the study period (Fig. 3d). Across all treatment groups and timepoints, fewer than 10% of subjects reported that the medication strength was "too strong" (Fig. 3d).

Safety Profile

By the end of treatment period 1 (6 months), the number of subjects in each treatment group who reported a TEAE was similar (Table 4). Although rare, serious TEAEs were more common with LEM5 and LEM10 than with placebo. Overall, 2.2%, 5.8%, and 10.7% of subjects in the placebo, LEM5, and LEM10 groups, respectively, had a TEAE leading to study drug withdrawal. The most common TEAEs were somnolence, nasopharyngitis, and headache. Of

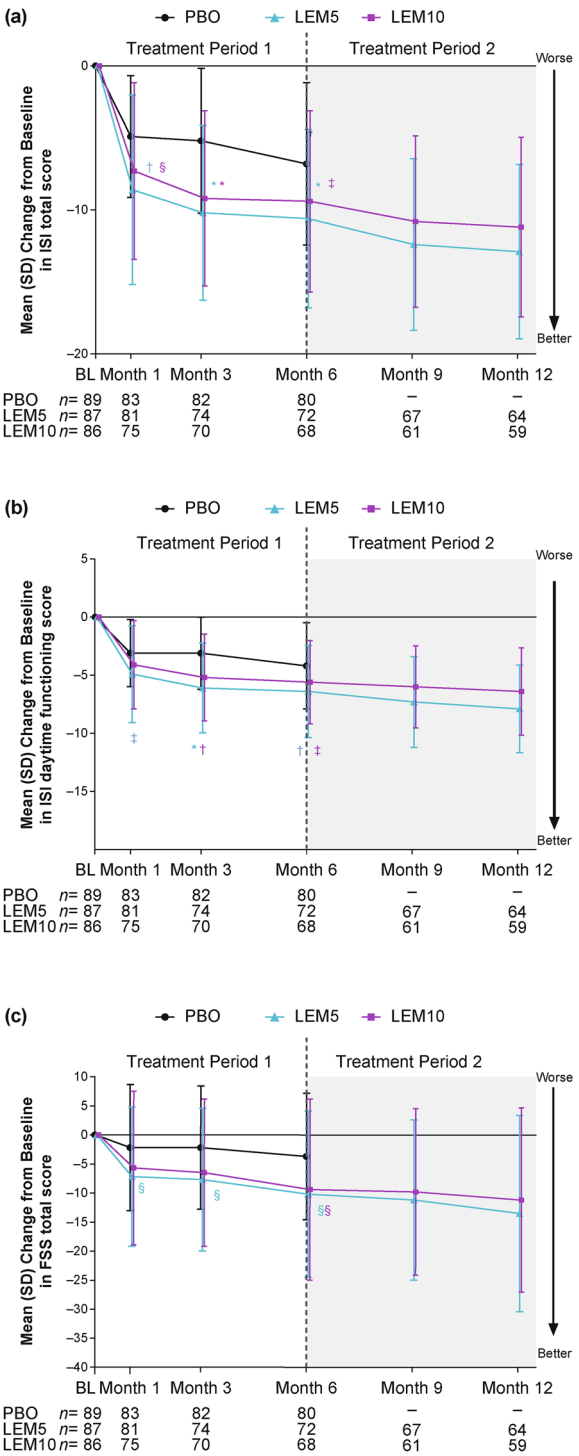


Fig. 2 Change from BL in ISI total score (**a**), ISI daytime functioning score (**b**), and FSS total score (**c**) from month 1 through month 12 in adults ≥ 65 years of age in Study 303. For ISI and FSS in treatment period 1, *P*-values are based on the LSM treatment difference for LEM minus placebo (LEM − PBO) using an MMRM analysis with factors for region, treatment, visit (timepoint), and treatment and treatment-by-visit interaction as fixed effects and the baseline score value as a covariate. Missing values were not imputed and assumed to be missing at random. For the data on or after month 9, the analysis includes only the subjects initially randomized to LEM5 or LEM10. Mean FSS total scores for the subgroup were presented in Chepke et al. [28]. Significant differences are indicated by the asterisk ($^{*}P < 0.0001$ vs. PBO), dagger ($^{\dagger}P < 0.001$ vs. PBO); double dagger ($^{\ddagger}P < 0.01$ vs. PBO); and section sign ($^{\S}P < 0.05$ vs. PBO). *BL* Baseline, *FSS* Fatigue Severity Score, *ISI* Insomnia Severity Index, *LEM* lemborexant, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *LSM* least squares mean, *MMRM* mixed effect model repeated measure, *PBO* placebo, *SD* standard deviation

these, somnolence was more common in the LEM groups compared with placebo. However, all TEAEs of somnolence were considered to be mild or moderate (Table 4). Among other TEAEs of interest, falls (placebo: $n = 3$ (3.4%); LEM5: $n = 1$ [1.2%]; LEM10: $n = 1$ [1.2%]) and cognitive deficits (placebo: $n = 0$; LEM5: $n = 0$; LEM10: $n = 2$ [2.4%; confusion state]) were not commonly reported as TEAEs through 6 months. During the second 6 months of treatment, the incidence of TEAEs among LEM-treated adults ≥ 65 years of age was similar to that of the SAS for the same treatment period (ESM Table S2) [20].

DISCUSSION

In adults ≥ 65 years of age with insomnia, LEM provided benefit on subject-reported sleep outcomes within the first week of treatment through 6 months and sustained through 12 months. These results are consistent with the results from the FAS in Study 303, where significant benefits of LEM versus placebo on subjective sleep onset and subjective sleep

Table 3 Insomnia Severity Index responder and remitter analysis in adults ≥ 65 years of age

Insomnia Severity Index responder and remitter analysis	PBO (*n* = 89) Yes/no/missing	LEM5 (*n* = 87) Yes/no/missing	LEM10 (*n* = 86) Yes/no/missing
% Responders[a]			
Month 1	29.2/64.0/6.7	54.0/39.1/6.9*	43.0/44.2/12.8
Month 3	29.2/62.9/7.9	60.9/24.1/14.9*	54.7/26.7/18.6*
Month 6	44.9/44.9/10.1	60.9/21.8/17.2	55.8/23.3/20.9
Month 9	–	64.4/12.6/23.0	53.5/17.4/29.1
Month 12	–	60.9/12.6/26.4	53.5/15.1/31.4
% Remitters ISI < 10[b]			
Month 1	13.5/79.8/6.7	39.1/54.0/6.9*	29.1/58.1/12.8†
Month 3	19.1/73.0/7.9	43.7/41.4/14.9*	39.5/41.9/18.6*
Month 6	29.2/60.7/10.1	48.3/34.5/17.2§	38.4/40.7/20.9
Month 9	–	57.5/19.5/23.0	44.2/26.7/29.1
Month 12	–	56.3/17.2/26.4	39.5/29.1/31.4
% Remitters ISI < 8[b]			
Month 1	9.0/84.3/6.7	31.0/62.1/6.9*	20.9/66.3/12.8§
Month 3	15.7/76.4/7.9	31.0/54.0/14.9§	26.7/54.7/18.6
Month 6	18.0/71.9/10.1	39.1/43.7/17.2†	29.1/50.0/20.9
Month 9	–	46.0/31.0/23.0	33.7/37.2/29.1
Month 12	–	43.7/29.9/26.4	33.7/34.9/31.4

CHM Cochran–Mantel–Haenszel, *ISI* Insomnia Severity Index, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *PBO* placebo

*$P < 0.002$ vs. placebo using the CHM test; †$P < 0.01$ vs. placebo using the CHM test; §$P < 0.05$ vs placebo using the CHM test

[a]Responders are the percentage of subjects with a decrease from baseline of ≥ 7 points in ISI total score

[b]Remitters are the percentage of subjects who achieved remission from insomnia based on ISI total score < 10 or < 8

maintenance were observed through 6 months and sustained over 1 year [19, 20, 28].

LEM was well tolerated in adults ≥ 65 years of age over 12 months of treatment. The safety profile in older adults was similar to the overall population in Study 303 [19, 20] and to that observed in Study E2006-G000-304 (SUNRISE-1), a phase 3 study in adults ≥ 55 years of age with insomnia [29]. Most occurrences of somnolence, which was the most common TEAE in the ≥ 65-years-of-age subgroup, were mild in severity. In adults > 55 years of age with

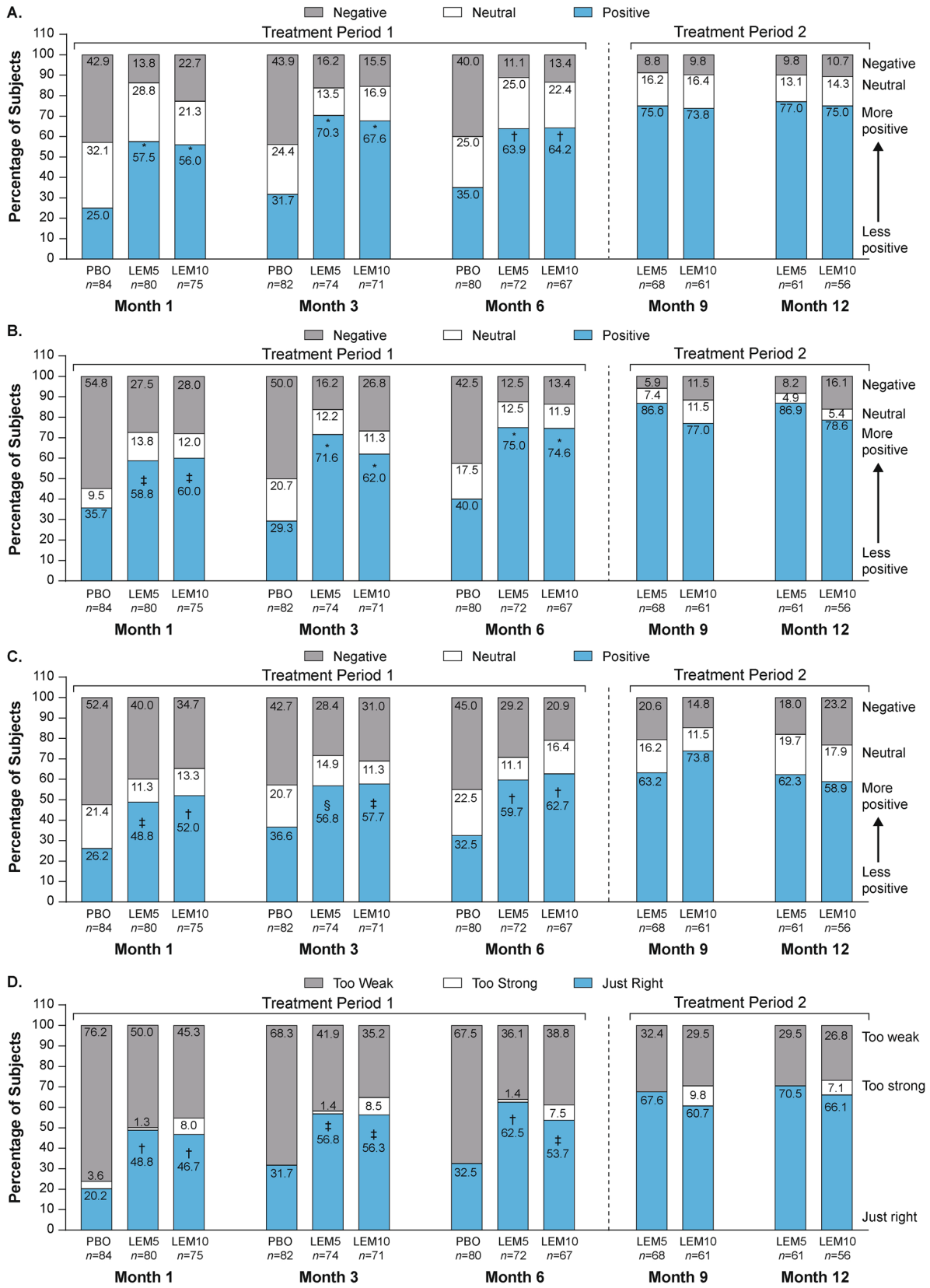
insomnia, the ISI daytime function score was significantly improved after 1 month of treatment with both LEM5 and LEM10 [29]. In the analyses presented here, the ISI daytime functioning score was significantly improved in both LEM treatment groups at month 3. Similarly, improvement in the ISI total score was evident after 1 month of treatment and was sustained through 12 months. In another study in healthy subjects ≥ 65 years of age, bedtime administration of LEM5 and LEM10 did not cause significant next-morning residual effects on postural stability or cognitive performance [18]. Furthermore, a study of healthy older adults demonstrated no significant deleterious effect on the ability to drive using an on-the-road driving test in the morning following single or multiple doses of LEM compared with placebo [30].

In addition to improvements in sleep onset and maintenance, subjects treated with LEM reported significantly larger changes from baseline in morning alertness compared with placebo. Also, LEM5 and LEM10 treatments had a significant benefit over placebo at the end of month 6, with subjects reporting larger changes from baseline in fatigue that were sustained through month 12. In the Study 303 FAS analysis, significant reduction in fatigue was reported for both LEM groups at the end of month 3 and sustained through month 12 [28].

Use and selection of insomnia medication should be carefully considered, especially among older adults. Although pharmacologic recommendations for insomnia disorder differ slightly across guidelines, benzodiazepines and sedative-hypnotic Z-drugs are often prescribed. According to Beers Criteria, benzodiazepines and Z-drugs are generally not recommended for insomnia disorder due to their association with cognitive impairment (benzodiazepines) and with delirium, falls, fractures, and motor vehicle crashes in older adults (benzodiazepines and Z-drugs) [14]. In April 2019, the US Food and Drug Administration required Boxed Warnings on the labels of some Z-drug sedative-hypnotic agents (zopiclone, zaleplon, and zolpidem) alerting consumers to the risk of rare but serious injuries due to complex sleep behaviors [31]. In 2020, the Boxed Warning label on benzodiazepine products was updated to alert consumers about the potential for abuse, addiction, physical dependence, and withdrawal reactions, particularly relevant for older adults as age is a potential risk factor for long-term or high-dose benzodiazepine use or dependence [32]. It is notable, therefore, that the proportion of those reporting LEM strength as "too weak" did not increase over 12 months, indirectly suggesting that tolerance did not develop.

With the shift in worldwide demographics towards an aging population [33], it is important to understand the efficacy and safety of medications in older individuals. A strength of this post hoc analysis is that it includes data from a global, multicenter, randomized, double-blind, placebo-controlled clinical trial of which one-fourth of the study population with insomnia were ≥ 65 years of age [19, 20]. The study design illustrates the benefits of LEM on both early and long-term subjective sleep parameters in older adults (≥ 65 years of age), which confirms results in the FAS [19, 20].

This study has some limitations. Subjects received a fixed dose of LEM, and dose titration was not allowed. Thus, subjects could not decrease their dose from LEM10 to LEM5 if they perceived the dose as "too strong" or if it was associated with somnolence; nor could they increase their dose from LEM5 to LEM10 if efficacy with the lower dose was insufficient. Most older adults in this post hoc analysis were White and female, but there was diversity in the overall study population. It should be noted that relevant effects of age, gender, or race (Asian [Japanese] versus White) on LEM pharmacokinetics and pharmacodynamics or safety were not identified in phase 1 studies involving healthy adults [34].


A.
Negative
Neutral
Positive
Treatment Period 1
Treatment Period 2
Percentage of Subjects
Negative
Neutral
More positive
Less positive
PBO n=84
LEM5 n=80
LEM10 n=75
PBO n=82
LEM5 n=74
LEM10 n=71
PBO n=80
LEM5 n=72
LEM10 n=67
LEM5 n=68
LEM10 n=61
LEM5 n=61
LEM10 n=56
Month 1
Month 3
Month 6
Month 9
Month 12
B.
Negative
Neutral
Positive
Treatment Period 1
Treatment Period 2
Percentage of Subjects
Negative
Neutral
More positive
Less positive
Month 1
Month 3
Month 6
Month 9
Month 12
C.
Negative
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Treatment Period 1
Treatment Period 2
Percentage of Subjects
Negative
Neutral
More positive
Less positive
Month 1
Month 3
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Month 9
Month 12
D.
Too Weak
Too Strong
Just Right
Treatment Period 1
Treatment Period 2
Percentage of Subjects
Too weak
Too strong
Just right
Month 1
Month 3
Month 6
Month 9
Month 12

◂**Fig. 3** Percentage of LEM-treated subjects who reported a positive, neutral, or negative effect of study drug over time for PGI-I items: **a** "medication helped me sleep" (item 1), **b** "time to fall asleep" (item 2), **c** "total sleep time" (item 3), and **d** "appropriateness of medication strength" (item 4). Percentages are based on the total number of subjects with non-missing values in the relevant treatment group. *P*-values vs. PBO are based on the Chi-square test comparing "positive" to "neutral" and "negative" response categories combined. For the data on or after month 9, the analysis includes only the subjects initially randomized to LEM5 or LEM10. Significant differences are indicated by the asterisk ($^{*}P < 0.0001$ vs. PBO), dagger ($^{\dagger}P < 0.001$ vs. PBO); double dagger ($^{\ddagger}P < 0.01$ vs. PBO); and section sign ($^{\S}P < 0.05$ vs. PBO). *LEM* lemborexant, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *PBO* placebo, *PGI-I* Patient Global Impression-Insomnia

CONCLUSIONS

The results reported in Study 303 support LEM as a potential treatment in adults ≥ 65 years of age with insomnia disorder. LEM provided significant benefit versus placebo on subject-reported measures of sleep onset and sleep maintenance that was noted within a few days of treatment initiation and persisted over 12 months. At Month 6, both LEM5 and LEM10 reduced fatigue, and these effects were sustained to month 12 (i.e., end of study). A reduction in insomnia severity preceded fatigue improvement, with both LEM treatment groups reporting insomnia improvement as measured by the ISI total score by month 1. In addition,

Table 4 Treatment-emergent adverse events in adults ≥ 65 years of age during treatment period 1

Category, *n* (%)[a]	**PBO (*n* = 89)**	**LEM5 (*n* = 86)**	**LEM10 (*n* = 84)**
Any TEAE[b]	59 (66.3)	57 (66.3)	46 (54.8)
Treatment-related	13 (14.6)	22 (25.6)	28 (33.3)
Severe	1 (1.1)	7 (8.1)	2 (2.4)
Serious	1 (1.1)	3 (3.5)	3 (3.6)
TEAE leading to study drug withdrawal	2 (2.2)	5 (5.8)	9 (10.7)
TEAE leading to interruption of study drug	1 (1.1)	3 (3.5)	3 (3.6)
Death	0	0	0
TEAE occurring in ≥ 5% in either LEM group			
Somnolence	0	7 (8.1)	16 (19.0)
- Mild	0	5 (5.8)	13 (15.5)
- Moderate	0	2 (2.3)	3 (3.6)
- Severe	0	0	0
Nasopharyngitis	8 (9.0)	5 (5.8)	6 (7.1)
Headache	6 (6.7)	8 (9.3)	1 (1.2)

AE Adverse event, *LEM* lemborexant, *LEM5* lemborexant 5 mg, *LEM10* lemborexant 10 mg, *PBO* placebo, *TEAE* treatment-emergent adverse event

[a]Percentages are based on the total number of subjects in the relevant treatment group

[b]TEAE is defined as an AE with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. For each row category, a subject with ≥ 2 AEs in the category is counted only once

most subjects reported that LEM had a positive impact on sleep. There was no evidence of tolerance to either LEM dose, as evidenced indirectly by examining the proportion of subjects over time who rated its strength as "too weak." There was no evidence of rebound insomnia during the 2-week off-treatment follow-up period. LEM was generally well tolerated over 12 months of treatment, and its safety profile in this older aged subgroup was similar to that of the overall study population [19, 20]. These data may help inform clinician decisions for prescribing pharmacotherapy for insomnia disorder and provide a safe treatment option for people ≥ 65 years of age.

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Author Contributions. Margaret Moline was responsible for conception and design of the work described herein. Kate Pinner performed the statistical analyses. Valerie Arnold, Sonia Ancoli-Israel, Thien Thanh Dang-Vu, Kazuo Mishima, Kate Pinner, Manoj Malhotra, and Margaret Moline reviewed and critically revised the manuscript for important intellectual content, interpreted the data, approved the final version of the manuscript, and agree 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.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Valerie Arnold received honoraria from Ironshore, Neos, Rho, and Shire; served as a consultant for Ironshore; served on the speaker's bureau for Takeda; and holds Supernus stock and/or stock options. Sonia Ancoli-Israel served as a consultant/advisory board member for Biogen, Eisai, Idorsia, Merck, NeuroVigil, Inc., Puretech, and Wesper. Thien Thanh Dang-Vu served as consultant and received speaker honoraria from Eisai, Paladin Labs, Idorsia, and Jazz Pharmaceuticals; and received research grants from Paladin Labs and Jazz Pharmaceuticals. Kazuo Mishima received speaker honoraria from Eisai Co., Ltd., MSD Inc., and Takeda Pharmaceutical Co., Ltd.; and received research grants from Eisai Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Margaret Moline is an employee of Eisai Inc. Kate Pinner is an employee of Eisai Ltd. Manoj Malhotra is a former employee of Eisai Inc. and is affiliated with Harlem Hospital, New York (NY, USA).

Ethical Approval. The protocol, protocol amendments or revisions, and informed consent form for Study 303 were approved by a qualified institutional review board and/or independent ethics committee. The study was conducted in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments or comparable standards. The study is registered on ClinicalTrials.gov (NCT02952820) and on EudraCT (2015–001463-39). Additional study details, including site information, can be found at https://clinicaltrials.gov/study/NCT02952820.

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