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ORIGINAL RESEARCH

Perception of Lemborexant Effectiveness as Assessed by the Patient Global Impression–Insomnia Questionnaire

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Objective: Using data from a clinical study of lemborexant, evaluate responses to the Patient Global Impression–Insomnia (PGI-I) questionnaire, a simple 4-item questionnaire that assesses patients' perceptions of the effects of medication on sleep, which may help evaluate clinically meaningful changes from the patient's perspective.

Methods: Study E2006-G001-303, a 12-month, placebo (PBO)-controlled (first 6 months) Phase 3 study in adults with insomnia disorder, randomized subjects (1:1:1) to lemborexant 5 mg (LEM5; n=316), 10 mg (LEM10; n=315), or PBO (n=318). The second 6 months are not presented here. PGI-I results were analyzed post hoc in relation to patient-reported (subjective) sleep-onset latency (sSOL) and total-sleep-time (sTST).

Results: At 6 months: 67.3% (LEM5) and 68.8% (LEM10) of subjects reported positive effects of medication helping them sleep versus 45.0% (both $p<0.0001$) with PBO. Positive effects on "time to fall asleep" were reported by 72.8% (LEM5) and 73.1% (LEM10) versus 46.1% with PBO ($p<0.0001$), and 58.0% (LEM5) and 62.0% (LEM10) reported positive effects on sleep duration versus 39.9% with PBO ($p<0.0001$). Subjects reporting positive effects on "time to fall asleep" had greater change from baseline (CFB; improvement) at 6 months in median sSOL (in minutes; LEM5= −26.8; LEM10= −32.1; PBO= −17.5; $p<0.01$) versus those reporting negative effects (LEM5= −9.1; LEM10= −10.4; PBO= −8.6; LEM5 vs PBO, $p=0.52$; LEM10 vs PBO, $p=0.69$). For sTST (in minutes) at 6 months, mean CFB tended to be greater for subjects reporting positive (LEM5=81.2, LEM10=93.2, PBO=74.8; LEM5 vs PBO, $p=0.28$; LEM10 vs PBO, $p=0.18$) versus negative (LEM5=46.4, LEM10=35.0, PBO=38.6; LEM5 vs PBO, $p=0.44$; LEM10 vs PBO, $p=0.52$) effects, although this was not statistically significant.

Conclusion: Patient impressions of the effects of lemborexant were positive based on the PGI-I and reflected improvements in subjective sleep outcome measures, indicating that the brief PGI-I tool may be useful in clinical practice.

Plain Language Summary: People with chronic insomnia, a common sleep disorder, have trouble falling asleep and/or staying asleep 3 or more times per week for at least 3 months. Insomnia treatments should improve sleep when measured objectively but should also improve sleep from the patient's perspective. The Patient Global Impression–Insomnia (PGI-I) is a simple 4-item questionnaire that assesses a patient's perceived efficacy of their sleep medication. Lemborexant is a medicine used to treat insomnia. This study evaluated the patient's view of the success of lemborexant treatment over time. There were 316, 315, and 318 people with chronic insomnia in the lemborexant 5 mg, lemborexant 10 mg, and no active treatment (placebo) groups, respectively, in this study. People treated with lemborexant reported more positive views of their medication on the PGI-I compared with those treated with placebo. These positive impressions of lemborexant on the PGI-I were associated with improvements in related subjective measurements of sleep. These results indicate that the PGI-I is a tool that may help assess whether an insomnia treatment is working from the patient's viewpoint.

Keywords: insomnia, orexin receptor antagonist, sleep, patient-reported outcome measure

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Introduction

Insomnia is a highly prevalent sleep-wake disorder characterized by difficulty initiating and/or maintaining sleep. Reduced sleep time from insomnia impacts daytime functioning and is associated with impairment of memory and alertness, as well as diminished quality of life.[1–6]

The first-line treatment for insomnia is cognitive behavioral therapy for insomnia (CBT-I).[7–9] When CBT-I is not successful or is unavailable, pharmacological therapy, including sedative-hypnotics (benzodiazepines and Z-drugs, such as zolpidem), may be used.[8,10] However, the use of these agents is associated with increased risk of tolerance and dependence, falls, respiratory depression, memory impairment, aberrant nocturnal behavior, and rebound insomnia following withdrawal.[9,11,12] Long-term, effective, and tolerable insomnia treatments are needed.

Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved in multiple countries, including the United States, Japan, Canada, Australia, and several Middle Eastern and Asian countries, for the treatment of adults with insomnia. DORAs promote wakefulness and regulate sleep/wake function by blocking orexin receptors 1 and 2, thereby promoting sleep.[13]

When evaluating the overall effectiveness of an insomnia treatment, perceived efficacy is critical to gaining insight into what is important and meaningful to the patient. A successful insomnia treatment should demonstrate improvement from the patient's perspective in addition to the improvements measured by objective techniques, such as polysomnography. Accurate and reliable assessment of the degree of improvement is important for guiding decisions when evaluating treatment effectiveness and adherence in clinical practice. At the same time, determining efficacy in clinical practice should not be burdensome and should be efficiently achieved.

Despite the many instruments available to screen for insomnia and evaluate treatment outcomes (eg, sleep diary,[14] Insomnia Severity Index [ISI],[15] Pittsburgh Sleep Quality Index,[16] Insomnia Symptom Questionnaire,[17] and Athens Insomnia Scale[18]), many are not practical in routine high-volume clinical practice (ie, an accurate and efficient tool that can be used ubiquitously and without cost to screen/evaluate insomnia in clinical practice).[19] The time frame, number of items, response structure, and patient burden vary among instruments, and each instrument has strengths and limitations.[19]

The Patient Global Impression–Insomnia (PGI-I) is a 4-item questionnaire used to evaluate patients' perceptions of the effects of medication on their sleep during or at the end of treatment relative to their sleep prior to treatment initiation.[20,21] Item 1 (study medication helped sleep), item 2 (study medication decreased time to fall asleep), and item 3 (study medication increased total sleep time) of the PGI-I are rated by subjects on a 3-point scale (1 = positive medication effect, 2 = neutral medication effect, 3 = negative medication effect), and item 4 (appropriateness of medication strength) is rated on a different 3-point scale (1 = too strong, 2 = just right, 3 = too weak).The PGI-I could be easy to administer in clinical practice as it uses few items, all typical to office visit questions; this may be helpful in incorporating more standardized validated assessments into clinical practice for making clinical decisions regarding changes in or maintenance of a patient's current dosing regimen. The PGI-I could also be utilized in more general patient populations, including primary care, where most patients with insomnia are treated.[22] The PGI-I is not currently a standard assessment for insomnia in clinical practice, and although the PGI-I has been used in previous insomnia studies of zolpidem, these studies did not examine the correlation between patient-reported sleep diary data and the PGI-I.[20,21]

The PGI-I was a prespecified exploratory endpoint in a global, phase 3, randomized, double-blind clinical trial (study E2006-G000-303 [Study 303/SUNRISE-2, NCT02952820]) of LEM in adults with insomnia disorder. In Study 303, LEM 5 mg (LEM5) and LEM 10 mg (LEM10) provided significant benefit compared with placebo (PBO) on patient-reported (subjective) measures of sleep onset and sleep maintenance in subjects with insomnia disorder.[23] This treatment benefit was evident within 1 week of the initiation of treatment and over the 6-month placebo-controlled treatment period.[23]

Here, we report comparisons of PGI-I responses between treatment groups in Study 303 for the first 6-month, PBO-controlled period. In addition, positive, neutral, and negative subject responses to PGI-I items 1–3 were examined with respect to patient-reported (subjective) sleep onset latency (sSOL) and subjective total sleep time (sTST), which are measured in minutes based on sleep diary data. This allows both further validation of the PGI-I instrument as well as an understanding of its sensitivity to the newer class of orexin antagonists, which are increasingly being utilized in clinical practice. Subjects' responses on the appropriateness of medication strength recorded in the PGI-I were also assessed to

provide a standardized measure that could be used in clinical practice to evaluate the need for appropriate treatment adjustments without the use of lengthier patient-reported outcome measures.

Overall, the goals of these analyses were to evaluate the patient's view of the success of insomnia treatment over time and provide guidance to assist clinicians in judging whether patients have achieved an expected and clinically meaningful magnitude of improvement.

Materials and Methods

Participants

Complete enrollment criteria for Study 303 have been previously described.[23] Briefly, study subjects were male and female adults (aged ≥18 years) with insomnia disorder as described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.[24] Subjects had a reported history of sSOL >30 minutes and/or subjective wake after sleep onset (sWASO) >60 minutes at least three times per week in the previous 4 weeks and an ISI score >15.[15] Inclusion and exclusion criteria have been previously reported.[23] Notably, patients with obstructive sleep apnea, determined based on the STOP-Bang assessment,[25] were not eligible to participate in this study.

Study Design

Study 303 was a 12-month, randomized, double-blind, parallel-group, fixed-dose, global phase 3 trial of subjects receiving LEM who underwent screening and a PBO run-in period lasting approximately 2 weeks, after which subjects were randomized (1:1:1) to LEM5, LEM10, or PBO for the first 6 months of the study (treatment period 1).[23] For the second 6 months (treatment period 2; not reported here), subjects from the PBO group were rerandomized (1:1) to LEM5 or LEM10, and subjects previously receiving LEM continued to receive LEM at the same dose.

The primary efficacy endpoint of Study 303 was mean change from baseline in sSOL at the end of month 6. The key secondary endpoints were mean changes from baseline in subjective sleep efficiency (sSE) and sWASO at the end of month 6. These endpoints have been previously reported.[23]

The study protocol was approved by the lead institutional review board (Quorum Review IRB, Seattle, WA, USA) and additional institutional review boards and independent ethics committees (Supplementary Table 1). The study adhered to Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations. All study participants provided written informed consent prior to screening.[23] Additional details of the study design have been previously reported.[23]

PGI-I

The PGI-I was administered at the end of months 1, 3, and 6 during treatment period 1. As the PGI-I is designed to assess the global impression of the effects of a study drug or medication strength at pre-specified time points, it is not administered at baseline.

Items 1–3 of the PGI-I are related to patient perceptions of the effects of the study drug on sleep, and item 4 is related to perceived medication strength. The four items included in the PGI-I include item 1 (study medication helped sleep), item 2 (study medication decreased time to fall asleep), item 3 (study medication increased total sleep time), and item 4 (appropriateness of medication strength) (Table 1). PGI-I items 1–3 are rated by subjects on a 3-point scale (1 = positive medication effect, 2 = neutral medication effect, 3 = negative medication effect; Table 1). PGI-I item 4 is rated on a different 3-point scale (1 = too strong, 2 = just right, 3 = too weak; Table 1).

Statistical Analyses

For the original statistical analysis plan, missing values for the primary and key secondary endpoints (sSOL, sSE, and sWASO) were imputed using complete case missing value pattern imputation and assumed to be missing not at random.[23] Other endpoints were analyzed using a mixed-effects model of repeated measures (MMRM) assuming missing at random.

The PGI-I was evaluated for the full analysis set (FAS), defined as study subjects who received at least one dose of study drug and at least one post-dose primary efficacy measurement (change from baseline in sSOL). Each PGI-I item

Table 1 Patient Global Impression–Insomnia (PGI-I) scale[20]

PGI-I Item	Scale
Item 1: Study medication helped sleep	1 = Positive medication effect 2 = Neutral medication effect 3 = Negative medication effect
Item 2: Study medication decreased time to fall asleep	1 = Positive medication effect 2 = Neutral medication effect 3 = Negative medication effect
Item 3: Study medication increased total sleep time	1 = Positive medication effect 2 = Neutral medication effect 3 = Negative medication effect
Item 4: Study medication strength	1 = too strong 2 = just right 3 = too weak

was analyzed separately. For each response level, percentages were based on the total number of subjects with non-missing values in the relevant treatment group.

In comparisons between treatment groups for PGI-I items 1–3, p-values for LEM versus PBO at months 1, 3, and 6 were based on a chi-square test comparing the number of positive responses with the number of neutral or negative responses combined. For PGI-I item 4, the number of "just right" responses, indicating perception of an appropriate dose, was compared with "too weak" or "too strong" responses (both responses indicate perception of a non-appropriate dose) combined. Missing values were not imputed.

In assessing PGI-I responses in relation to sleep measures (changes from baseline) in patient-reported (subjective) sleep measures, sSOL (estimated minutes from the time that the participant attempted to sleep until sleep onset) and sTST (derived minutes of sleep from sleep onset until the time the participant stopped trying to sleep for the night) were assessed using an MMRM analysis, with factors for age, region, visit (time point), treatment, and treatment-by-visit interaction as fixed effects and the baseline value as a covariate. Missing values for sSOL were imputed using multiple imputation and assumed to be missing not at random. Missing values for sTST were not imputed and were assumed to be missing at random. A log transformation was used for sSOL values, and statistical comparisons were conducted using the least squares geometric means (LSGM) due to lack of normal distribution.

Analyses of the percentage of responders of sTST (defined as sTST of ≥7 hours) at month 6 were performed using the Cochran-Mantel-Haenszel test, stratified by region and age group. Missing values were considered non-responders (defined as sTST of <7 hours).

Clinically Meaningful Changes in Sleep Measures Related to PGI-I Items 2 and 3

To evaluate the magnitude of change perceived by a subject as clinically meaningful, additional analyses examined changes from baseline in sleep parameters relative to subject responses to PGI-I items 2 (study medication decreased/increased time to fall asleep) and 3 (study medication increased/decreased total sleep time). These analyses included median change from baseline in sSOL separately for subjects by report of a positive, neutral, or negative effect of medication on PGI-I item 2 at month 6. In addition, the mean change from baseline in sTST was assessed separately for subjects by report of positive, neutral, or negative effect of treatment on PGI-I item 3 at month 6.

Change from Baseline in Sleep Measures Related to PGI-I Item 4

The relationship between changes in sleep and subjects' perceptions of the appropriateness of medication strength (PGI-I item 4) was assessed by analyzing sSOL and sTST at baseline and month 6 by treatment group (PBO, LEM5, and LEM10) and response to item 4 ("too weak" or "just right"). Change from baseline at month 6 in sleep measures was also calculated by treatment group and response to PGI-I item 4.

Safety

Safety assessments for Study 303 have been previously described.[23] Briefly, these assessments included monitoring of treatment-emergent adverse events (TEAEs) by investigators, clinical laboratory evaluations, recording of vital signs and weight, assessment of electrocardiograms, monitoring for suicidality, and physical examinations. TEAEs were also assessed by response to PGI-I item 4 to examine possible relationships between any TEAEs and subjects' perceptions of the appropriateness of medication strength.

Results

Subject Demographics

Full details of this study population have been previously reported.[23] The FAS comprised 949 subjects, with 316, 315, and 318 assigned to LEM5, LEM10, and PBO, respectively.[23] Baseline demographic characteristics, including baseline sSOL and sTST, were similar across treatment groups (Table 2). Subjects were mostly female (66.1%, 70.5%, and 67.9% for LEM5, LEM10, and PBO, respectively) and White (70.3%, 71.4%, and 73.0%, respectively).

Table 2 Baseline Demographic and Clinical Characteristics

	PBO (n=318)	LEM5 (n=316)	LEM10 (n=315)
Age[a], years			
Mean (SD)	54.5 (14.0)	54.2 (13.7)	54.8 (13.7)
Median (range)	56.0 (18–83)	55.0 (20–85)	55.0 (18–88)
Sex, n (%)			
Male	102 (32.1)	107 (33.9)	93 (29.5)
Female	216 (67.9)	209 (66.1)	222 (70.5)
Race, n (%)			
White	233 (73.0)	220 (70.3)	225 (71.4)
Black or African American	23 (7.2)	27 (8.5)	25 (8.3)
Asian	59 (18.6)	61 (19.3)	58 (18.4)
Other	4 (1.3)	6 (1.9)	6 (1.9)
BMI, mean (SD), kg/m2	27.2 (5.5)	27.3 (6.3)	27.2 (5.6)
ISI total score, mean (SD)	19.0 (3.1)	19.6 (3.3)	19.1 (3.4)
Sleep diary variables			
sSOL[b]			
n	316	314	312
Mean (SD), minutes	64.0 (45.2)	62.2 (45.7)	65.0 (44.0)
Median (range), minutes	55.9 (5.1–411.4)	53.6 (3.6–445.7)	55.7 (6.3–360.0)
Subjects with sSOL >30 minutes, n (%)	254 (79.9)	250 (79.1)	249 (79.0)
sTST[b]			
n	307	302	299
Mean (SD), minutes	304.3 (91.5)	315.5 (93.5)	306.9 (88.0)
Subjects with sTST <7 hours, n (%)	293 (91.8)	290 (91.8)	292 (93.0)

Notes: Percentages are based on the total number of subjects with non-missing values in the relevant treatment group. [a]Age was calculated at date of informed consent. [b]Baseline sleep diary variables are the mean of diary data entered on the last 7 mornings before the date of randomization; baseline sleep diary variables were analyzed with data handling rules applied.
Abbreviations: BMI, body mass index; ISI, Insomnia Severity Index; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; SD, standard deviation; sSOL, subjective sleep onset latency; sTST, subjective total sleep time.

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PGI-I

Items 1–3

During treatment period 1, significantly greater percentages of subjects treated with LEM5 and LEM10 reported that their study medication helped them sleep, decreased the time to fall asleep, and increased the TST compared with PBO at months 1, 3, and 6 (all comparisons, $p \leq 0.0001$; Figure 1A–C).

Item 4

A significantly greater percentage of subjects receiving LEM5 and LEM10 reported their study medication was "just right" compared with PBO at the end of months 1, 3, and 6 in response to item 4 (all comparisons, $p < 0.001$; Figure 1D). Over the duration of the study, the proportion of subjects reporting their medication as being "just right" increased and the proportion reporting their medication as being "too weak" decreased (Figure 1D). An increase in ratings of "too weak" over time would be an indirect indication of tolerance, and no such increase was observed with either LEM dose (Figure 1D). The highest percentage of "too weak" responses was in the PBO group, and the highest percentage of "too strong" responses was in the LEM10 group.

Clinically Meaningful Changes in Sleep Measures Based on PGI-I Items Related to Sleep Onset

At month 6, the change from baseline in sSOL was greater for all subjects who reported a positive response to medication on item 2 of the PGI-I compared with those who reported a neutral or negative perception. The median (1st, 3rd quartiles)

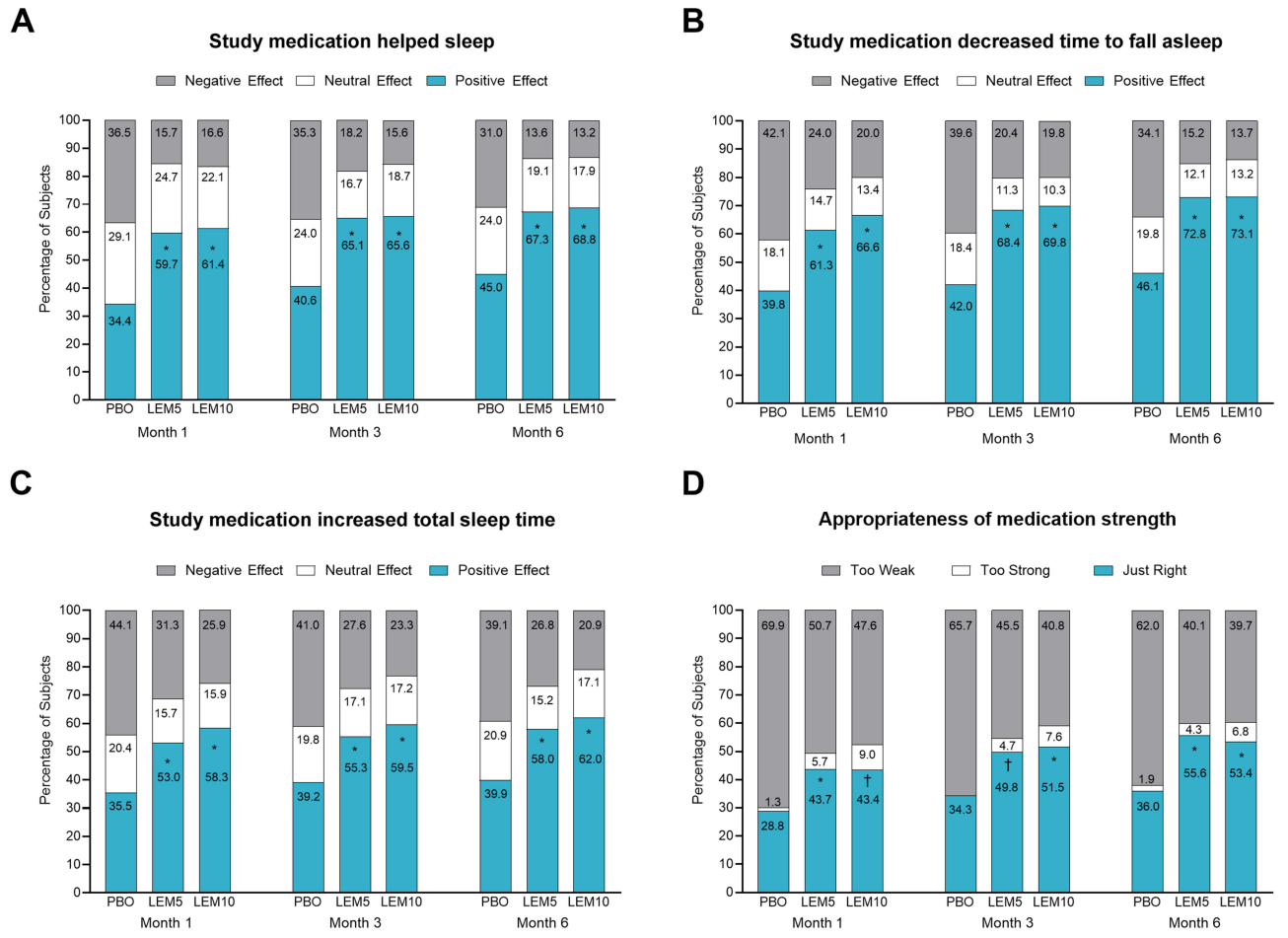

Figure 1 Percentage of subjects reporting a positive, neutral, or negative effect of study drug for Patient Global Impression–Insomnia items 1 (**A**), 2 (**B**), 3 (**C**), and 4 (**D**). *$p \leq 0.0001$; †$p < 0.001$. Percentages are based on the total number of subjects with non-missing values in the relevant treatment group. (**A–C**) p-value versus PBO is based on a chi-square test comparing positive to neutral and negative response categories combined. (**D**) p-value versus PBO is based on a chi-square test comparing "just right" to "too weak" and "too strong" response categories combined.

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

changes from baseline in sSOL were −26.8 (−47.9, −14.1) minutes with LEM5 ($p < 0.01$ versus PBO), −32.1 (−58.6, −15.0) minutes with LEM10 ($p < 0.01$ versus PBO), and −17.50 (−40.0, −4.3) minutes with PBO (Figure 2A, Table 3).

The median (1st, 3rd quartiles) changes from baseline in sSOL at month 6 in subjects reporting a neutral effect were −17.2 (−42.1, −7.4) minutes with LEM5, −25.6 (−54.2, 0.3) minutes with LEM10 ($p < 0.05$ vs PBO), and −10.4 (−33.2, 1.4) minutes with PBO (Figure 2A, Table 3). The median change from baseline in sSOL at month 6 in these subjects was smaller than in subjects reporting a positive effect.

Relatively little improvement in sSOL at month 6 was observed in subjects reporting a negative effect, and changes from baseline in sSOL were similar across treatment groups (median [1st, 3rd quartiles], −9.1 [−18.1, 0] minutes with LEM5, −10.4 [−25.1, 2.9] minutes with LEM10, and −8.6 [−23.6, 4.6] minutes with PBO; Figure 2A, Table 3).

Clinically Meaningful Changes in Sleep Measures Based on PGI-I Items Related to Sleep Duration

At month 6, subjects reporting a positive medication effect on item 3 of the PGI-I showed mean (standard deviation [SD]) changes from baseline sTST of 81.2 (66.7) minutes with LEM5, 93.2 (73.3) minutes with LEM10, and 74.8 (83.9) minutes with PBO (Figure 2B, Table 3).

The mean (SD) changes from baseline in sTST at month 6 in subjects reporting a neutral effect were 104.5 (103.1) minutes with LEM5 ($p < 0.01$ vs PBO), 87.7 (85.4) minutes with LEM10 ($p < 0.01$ vs PBO), and 40.8 (68.1) minutes with PBO (Figure 2B, Table 3). The mean change from baseline in sTST at month 6 in these subjects was smaller than in subjects reporting a positive effect for LEM10 and PBO but not LEM5.

Smaller improvement in sTST at month 6 was observed in subjects reporting a negative effect, and changes from baseline in sTST were similar across treatment groups (mean [SD], 46.4 [74.9] minutes with LEM5, 35.0 [82.6] minutes with LEM10, and 38.6 [63.5] minutes with PBO; Figure 2B, Table 3).

At baseline, approximately 92% of the subjects had sleep durations (sTST) <7 hours per night. At month 6, the proportion of subjects who were sTST responders (achieved an sTST of ≥7 hours) was significantly greater for subjects receiving either LEM5 (97/255, 38.0%; $p < 0.01$) or LEM10 (91/241, 37.8%; $p < 0.01$) compared with subjects receiving PBO (69/262, 26.3%).

Change from Baseline in Sleep Measures Related to PGI-I Item 4

For the subjects with a response of "just right" on PGI-I item 4 (appropriateness of medication strength), median reductions from baseline in sSOL at month 6 were greater across all treatment groups compared with subjects who responded "too weak" (Table 4). For the LEM5 and LEM10 groups, the median reductions from baseline in sSOL were −26.5 and −31.1 minutes, respectively, for subjects who responded "just right" −16.3 and −22.9 minutes for subjects who responded "too weak" and −27.7 and −45.0 minutes for subjects who responded "too strong". In subjects who responded "just right" or "too weak" the median reduction in sSOL from baseline was not significant for LEM5 versus PBO, but the reduction was significantly greater with LEM10 versus PBO ($p < 0.05$) (Table 4).

The LSM change from baseline in sTST for subjects who responded "just right" at month 6 was significantly greater with both doses of LEM (LEM5, 90.4 minutes; LEM10, 91.2) compared with PBO (72.2 minutes; $p < 0.05$ for both doses) (Table 4). The LSM change from baseline in sTST in subjects who responded "too weak" was lower for all treatment groups (51.1, 54.5, and 36.5 minutes with LEM5, LEM10, and PBO, respectively) (Table 4).

Safety

Detailed safety data collected during Study 303 have been previously reported.[26,27] Overall, the majority of reported TEAEs were mild or moderate in severity.[23]

For PGI-I item 4 (medication strength), subjects treated with either LEM5 or LEM10 who responded "too strong" reported higher rates of somnolence (LEM5: 18.2%; LEM10: 43.8%) compared with subjects who responded "just right" (LEM5: 9.8%; LEM10: 15.2%) or "too weak" (LEM5: 2.9%; LEM10: 4.3%). These higher rates of somnolence in subjects who responded "too strong" may account for the higher incidence of TEAEs reported in these subjects. In addition, across all response categories on PGI-I item 4, somnolence was reported in a greater percentage of subjects receiving LEM10 than LEM5 or PBO (Table 5). Additionally, responses of "too weak" did not increase for treatment groups over time, suggesting a low risk for LEM tolerance (Figure 1D). Most subjects (>92%) were 80% to ≤100% compliant with study medication.

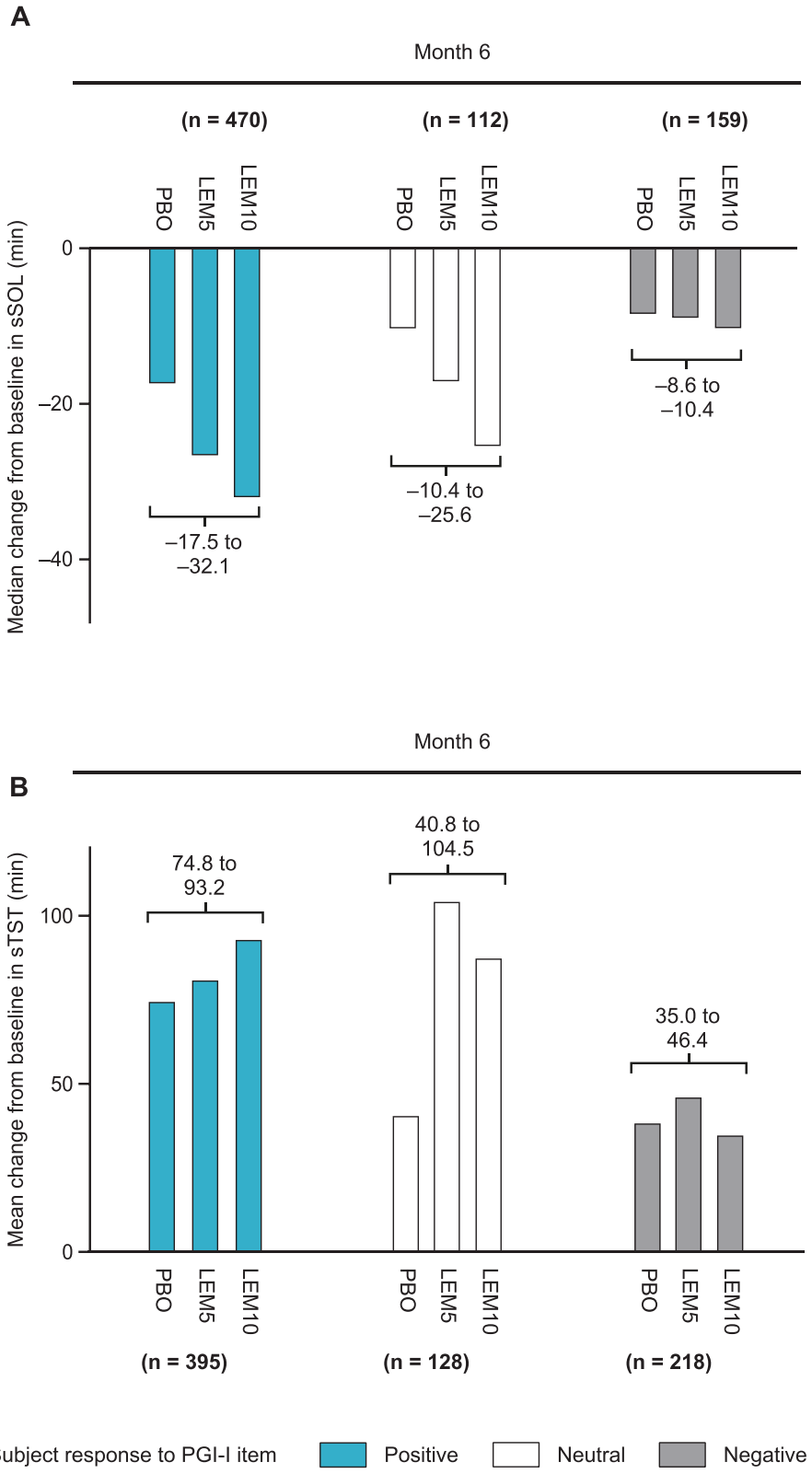

Figure 2 Changes from baseline at month 6 (**A**) subjective sleep onset latency (sSOL) by subject response to Patient Global Impression–Insomnia (PGI-I) item 2 (study medication decreased/increased time to fall asleep) and (**B**) subjective total sleep time (sTST) by subject response to PGI-I item 3 (study medication increased/decreased TST). **Abbreviations**: LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo: sSOL, subjective sleep onset latency; sTST, subjective total sleep time.

Table 3 Change from Baseline in Subjective Sleep Parameters by Response to PGI-I Items 2 and 3 at Month 6

		PBO	LEM5	LEM10
Median sSOL (1st, 3rd quartiles) at month 6, minutes				
Item 2: study medication decreased/increased time to fall asleep at month 6	Positive	−17.5 (−40.0, −4.3) (n=110)	−26.8 (−47.9, −14.1)† (n=178)	−32.1 (−58.6, −15.0)† (n=159)
	Neutral	−10.4 (−33.2, 1.4) (n=49)	−17.2 (−42.1, −7.4) (n=28)	−25.6 (−54.2, 0.3)* (n=27)
	Negative	−8.6 (−23.6, 4.6) (n=82)	−9.1 (−18.1, 0) (n=34)	−10.4 (−25.1, 2.9) (n=32)
Mean sTST (SD) at month 6, minutes				
Item 3: study medication increased/decreased TST at month 6	Positive	74.8 (83.9) (n=97)	81.2 (66.7) (n=139)	93.2 (73.3) (n=134)
	Neutral	40.8 (68.1) (n=49)	104.5 (103.1)† (n=32)	87.7 (85.4)† (n=35)
	Negative	38.6 (63.5) (n=88)	46.4 (74.9) (n=59)	35.0 (82.6) (n=41)

Notes: sSOL values were log transformed and statistical comparisons made using the LSGM. p-values are based on the mixed-effects model of repeated measures evaluating the LSGM treatment ratio (sSOL) or LSM treatment difference (sTST) between PBO and LEM, using factors for age group, treatment, visit, and treatment-by-visit interaction as fixed effects and the study baseline sSOL or sTST as a covariate. Missing values of sSOL were imputed using multiple imputation and were assumed to be missing not at random. Missing values of sTST were not imputed and were assumed to be missing at random. *$p < 0.05$ versus PBO; †$p < 0.01$ versus PBO at month 6.
Abbreviations: LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LSGM, least squares geometric mean; LSM, least squares mean; PBO, placebo; PGI-I, Patient Global Impression–Insomnia; SD, standard deviation; sSOL, subjective sleep onset latency; sTST, subjective total sleep time.

Table 4 Summary of Baseline and Month 6 Values and Change from Baseline at 6 Months for sSOL and sTST by Response at Month 6 to the PGI-I Medication Strength Question

	PBO (n=318)	LEM5 (n=316)	LEM10 (n=315)
Subjects responded "just right" at 6 months			
sSOL, minutes			
Baseline, median (1st, 3rd quartiles)	47.9 (31.4, 64.3) (n=90)	50.8 (35.7, 72.1) (n=137)	57.5 (36.4, 77.1) (n=118)
Month 6, median (1st, 3rd quartiles)	21.1 (14.3, 41.4) (n=90)	17.9 (11.3, 29.9) (n=138)	19.8 (10.0, 33.0) (n=118)
Change from baseline at month 6, median (1st, 3rd quartiles)	−15.5 (−37.0, −4.3) (n=90)	−26.5 (−52.1, −14.1) (n=137)	−31.1 (−53.7, −13.4)* (n=118)
sTST, minutes			
Baseline, mean (SD)	311.7 (90.9) (n=90)	330.8 (81.2) (n=134)	311.1 (88.8) (n=112)
Month 6, mean (SD)	385.3 (88.9) (n=90)	419.3 (65.3) (n=137)	402.8 (84.5) (n=114)
Change from baseline at month 6, LSM (SE)	72.2 (6.8) (n=90)	90.4 (5.6)* (n=137)	91.2 (6.1)* (n=114)
Subjects responded "too weak" at 6 months			
sSOL, minutes			
Baseline, median (1st, 3rd quartiles)	60.1 (36.4, 85.7) (n=149)	60.0 (33.4, 81.4) (n=95)	61.4 (37.9, 84.4) (n=87)
Month 6, median (1st, 3rd quartiles)	45.0 (21.6, 74.1) (n=151)	30.0 (17.8, 52.7) (n=96)	30.0 (16.5, 49.0) (n=88)
Change from baseline at month 6, median (1st, 3rd quartiles)	−10.0 (−32.4, 5.0) (n=149)	−16.3 (−36.2, −5.7) (n=95)	−22.9 (−50.7, −1.2)† (n=87)

(*Continued*)

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Table 4 (Continued).

	PBO (n=318)	**LEM5 (n=316)**	**LEM10 (n=315)**
sTST, minutes			
Baseline, mean (SD)	295.3 (93.0) (n=139)	300.2 (93.8) (n=87)	292.0 (85.9) (n=81)
Month 6, mean (SD)	334.2 (93.6) (n=144)	350.9 (100.7) (n=94)	348.5 (98.6) (n=86)
Change from baseline at month 6, LSM (SE)	36.5 (6.6) (n=139)	51.1 (8.4) (n=87)	54.5 (8.5) (n=81)
Subjects responded "too strong" at 6 months			
sSOL, minutes			
Baseline, median (1st, 3rd quartiles)	36.4 (23.4, 38.6) (n=5)	40.9 (34.3, 53.6) (n=10)	62.3 (39.3, 122.1) (n=15)
Month 6, median (1st, 3rd quartiles)	15.7 (10.8, 35.7) (n=5)	13.3 (5.7, 20.0) (n=10)	19.3 (8.6, 38.6) (n=15)
Change from baseline at month 6, median (1st, 3rd quartiles)	−14.1 (−25.7, 14.9) (n=5)	−27.7 (−39.1, −21.2) (n=10)	−45.0 (−82.9, −23.6) (n=15)
sTST			
Baseline, mean (SD)	387.9 (60.0) (n=5)	332.0 (50.1) (n=9)	294.5 (90.4) (n=15)
Month 6, mean (SD)	443.8 (65.8) (n=5)	394.3 (52.0) (n=9)	388.6 (92.4) (n=15)
Change from baseline at month 6, LSM (SE)	93.2 (41.3) (n=5)	72.3 (28.0) (n=9)	79.3 (19.8) (n=15)

Notes: sSOL values were log transformed and statistical comparisons made using the LSGM. p-values are based on the mixed-effects model of repeated measures evaluating the LSGM treatment ratio between PBO and LEM. Subjects with sSOL and sTST change from baseline data at month 6 but missing PGI-I data were excluded from this analysis (PBO, n=5; LEM5, n=3; LEM10, n=9). *$p < 0.05$ versus PBO; †$p < 0.01$ versus PBO.

Abbreviations: LEM, lemborexant; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LSGM, least squares geometric mean; LSM, least squares mean; PBO, placebo; PGI-I, Patient Global Impression–Insomnia; SD, standard deviation; SE, standard error; sSOL, subjective sleep onset latency; sTST, subjective total sleep time.

Table 5 Selected TEAEs Reported by Subject Response to PGI-I Item 4 (Medication Strength)

PGI-I item 4 response	**PBO (%)**	**LEM5 (%)**	**LEM10 (%)**
"Just right"	(n=93)	(n=143)	(n=125)
Any AE	61 (65.6)	87 (60.8)	70 (56.0)
Somnolence	0	14 (9.8)	19 (15.2)
Nasopharyngitis	15 (16.1)	15 (10.5)	12 (9.6)
Headache	5 (5.4)	15 (10.5)	6 (4.8)
"Too weak"	(n=160)	(n=103)	(n=93)
Any AE	99 (61.9)	64 (62.1)	59 (63.4)
Nasopharyngitis	19 (11.9)	9 (8.7)	10 (10.8)
Headache	12 (7.5)	8 (7.8)	10 (10.8)
Somnolence	0	3 (2.9)	4 (4.3)
"Too strong"	(n=5)	(n=11)	(n=16)
Any AE	4 (80.0)	9 (81.8)	12 (75.0)
Somnolence	2 (40.0)	2 (18.2)	7 (43.8)
Headache	1 (20.0)	2 (18.2)	1 (6.3)
Nasopharyngitis	0	1 (9.1)	2 (12.5)

Abbreviations: AE, adverse event; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; PGI-I, Patient Global Impression–Insomnia; TEAE, treatment-emergent adverse event.

Discussion

This study reports the results of the PGI-I from Study 303 and examines the relationship of PGI-I outcomes to patient-reported sleep changes in subjects with insomnia disorder receiving treatment with LEM compared with PBO.

Over the first 6 months of this phase 3 trial, significantly greater percentages of subjects treated with LEM5 or LEM10 reported positive effects of their study medication with respect to helping them sleep, reducing time to fall asleep, and increasing sleep duration compared with subjects treated with PBO. Across PGI-I items 1–3, LEM treatment effects were observed as early as month 1. Independent of treatment, subjects reporting positive responses on the PGI-I regarding sleep latency and sleep duration typically had the greatest overall changes from baseline in sSOL or sTST, respectively, whereas subjects reporting negative PGI-I responses had the smallest changes in sleep from baseline. Although there was some improvement in sleep parameters in the group that reported neutral or negative effects, it is possible that the treatment did not meet the expectation of improvement, hence the negative score. While additional research into this phenomenon would be valuable, it is beyond the scope of this study.

The majority of subjects reported that their medication decreased the time to fall asleep (item 2) and increased their sTST (item 3), as assessed at month 6. This shows that the PGI-I can provide insight into the magnitude of improvement for sleep onset (−17.5 to −32.1 minutes) and sTST (+74.8 to +93.2 minutes) that may be considered clinically meaningful from the patient's perspective. It is noteworthy that the inclusion criteria of Study 303 included sSOL of ≥30 minutes (and/or sWASO of ≥60 minutes) to identify subjects with insomnia.[28] The median sSOL at month 6 in subjects who reported a positive effect on falling asleep on the PGI-I was approximately 24 minutes for PBO and between 19 and 21 minutes for subjects receiving LEM5 and LEM10. Considering the high percentage of subjects with sSOL >30 minutes at baseline (79.1%, 79.0%, and 79.9% for LEM5, LEM10, and PBO, respectively; Table 2), this shows that most subjects receiving LEM5 or LEM10 who reported a positive medication effect could be considered as no longer having clinically important sleep onset difficulties, based on ≥30-minute sSOL threshold. In addition, the recommended sleep duration for adults is ≥7 hours (≥420 minutes);[29,30] the proportion of subjects achieving this threshold increased from baseline, and the mean sTST nearly reached this target at month 6 in subjects reporting a positive medication effect on PGI-I item 3.

A significantly greater percentage of subjects reported that their medication strength was "just right" (PGI-I item 4) with LEM versus PBO at months 1, 3, and 6. In addition, sleep measures improved to a greater extent in subjects responding "just right" compared with "too weak." These observations further suggest that subjects did not experience tolerance to LEM. Interestingly, only up to half of subjects across all time points and treatments felt their medication strength was "just right" and many felt it was "too weak." Similarly, a clinical trial of zolpidem reported that only around 55% of subjects indicated that their zolpidem medication strength was "just right" after 2 weeks of treatment;[20] this modest level of perceived efficacy may be due in part to the fixed-dose parallel-group design in Study 303.[26] It is also possible that a response of "too weak" at the highest dose of LEM may be an indication of lack of efficacy for that specific subject. In a clinical practice setting, subjects who reported that LEM5 was "too weak" could increase their dose, and subjects who reported LEM10 was "too strong" could decrease their dose. In clinical practice, allowing patients to increase or decrease their dose may influence their perceptions of the efficacy and tolerability of their therapy.

In Study 303, LEM was generally well tolerated.[26,27,31] The observed association between subject responses to PGI-I item 4 and the rate of TEAEs overall supports the usefulness of the PGI-I in assessing patients' experiences with insomnia medication. Furthermore, this shows the PGI-I to be sensitive to TEAEs in a pharmacological trial and indicates that the PGI-I can provide information about the safety and efficacy of a medication. In subjects across all treatment groups, and especially with LEM10, the highest rate of TEAEs, and somnolence in particular, occurred in subjects who reported that their medication was "too strong", although it should be considered that the total number of subjects reporting somnolence was small in all response groups. Moreover, while there were more subjects who reported an AE of somnolence in the LEM groups than placebo group, when the subject rated their assigned drug as "too strong" the reports of somnolence between PBO and LEM10 were similar. This may be because insomnia itself is associated with daytime sleepiness.

Although the PGI-I is not currently a standard assessment for insomnia in clinical practice, it has been utilized in previous reports from clinical trials.[20,21] The results from the current study can inform clinicians how much improvement (in minutes, as assessed via sleep diary data) is associated with a positive rating on the PGI-I. Sleep diaries can be used to assess the efficacy of a medication, but some patients may not wish to complete them. The PGI-I scale could be

a practical alternative that, if adopted as a standard assessment for insomnia, healthcare providers could routinely utilize in clinical practice at patient visits. Future studies should compare the PGI-I with other sleep scales, examine its reliability upon repeated use, and evaluate it in patients receiving other insomnia medications.

One limitation of the study was that missing data toward the end of the study could have impacted the estimate of the change in severity if subjects who discontinued were unbalanced with respect to having more favorable or unfavorable changes in severity. Another limitation, discussed above, relates to the fixed-dose design, which does not optimize the dose on an individual basis as in clinical practice and therefore could impact the ratings, especially of the strength of dose. Additionally, this post hoc analysis had a small number of subjects who reported the medication as "too strong", which may limit the interpretation of the findings related to PGI-I item 4.

Conclusions

The results from these analyses of the PGI-I from Study 303 suggest that the clinically significant improvements in subjective sleep onset and maintenance with LEM treatment were reflected in positive patient-reported perceptions of medication effects on the PGI-I. These findings from the PGI-I results from subjects receiving LEM for 6 months provide an understanding of how a patient's experience of his or her medication may be useful to clinicians in determining whether a treatment regimen is providing an expected benefit or if modifications to the treatment approach are warranted. The PGI-I items are likely to resonate with clinician assessments and are potentially easy to administer and interpret by non-sleep specialists, the clinicians typically treating insomnia. Therefore, the PGI-I could be easily used in general clinical practice settings, such as primary care, where most insomnia patients are initially treated.

Abbreviations

AE, adverse event; BMI, body mass index; CBT-I, cognitive behavioral therapy for insomnia; CFB, change from baseline; DORA, dual orexin receptor antagonist; FAS, full analysis set; ISI, Insomnia Severity Index; LEM, lemborexant; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LSGM, least squares geometric mean; LSM, least squares mean; PBO, placebo; PGI-I, Patient Global Impression–Insomnia; 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 event.

Data Sharing Statement

De-identified subject data that underlie the results reported in this article will not be made available, but summary information will be available on ClinicalTrials.gov. The data that support the findings of this study are not publicly available due to intellectual property restrictions and informed consent not including provisions for dissemination of the data; however, the data are available from the corresponding author upon reasonable request.

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Author Contributions

Conceptualization: CLD, JY, KP, MMo, MMa, Formal analysis: KP, Methodology: KP, MMo, Roles/Writing – original draft: CLD, JY, KP, MMo, MMa, Writing – review & editing: CLD, JY, KP, MMo, MMa. All authors have approved the final article, have agreed on the journal to which the article was submitted, and agreed to take responsibility and be accountable for the contents of the article.

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