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Transitioning insomnia patients from zolpidem to lemborexant: A multicenter, open-label study evaluating a next-dose transition approach to insomnia pharmacotherapy

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ABSTRACT

Objective: Few clinical studies have assessed real-world abrupt transitioning between insomnia medications. This study assessed strategies for directly transitioning patients from zolpidem tartrate (ZOL) immediate/extended release to the dual orexin receptor antagonist, lemborexant (LEM).

Methods: This randomized, open-label, multicenter study (Study 312; E2006-A001-312) enrolled 53 adults age ≥18 years with insomnia disorder and ≥1-month history of intermittent (3–4 nights/week) or frequent (≥5 nights/week) ZOL use. Subjects recorded their ZOL use in a 3-week Pretreatment Phase, followed by a 2-week Treatment Phase (TRT; Titration) during which ZOL was discontinued. Intermittent ZOL users transitioned to LEM 5 mg (LEM5), Cohort 1, and frequent ZOL users were randomized 1:1 to LEM5, Cohort 2A, or LEM 10 mg (LEM10), Cohort 2B. One dose adjustment was permitted during the TRT. Subjects completing the TRT could continue LEM in the 12-week Extension Phase (EXT). The primary outcome was proportion of subjects who successfully transitioned and remained on LEM at the end of the TRT.

Results: Most subjects (43 [81.1 %]) successfully transitioned to LEM (9 [90 %], 17 [81.0 %], and 17 [77.3 %] in Cohorts 1, 2A, and 2B, respectively). By the end of the EXT, 66.7 % in Cohort 1 and 60.0 % in Cohort 2A up-titrated to LEM10, whereas 41.2 % in Cohort 2B down-titrated to LEM5; 61.0 % were receiving LEM10 at study end. At the end of the TRT, more subjects taking LEM reported that it helped them return to sleep after waking, compared with those taking ZOL (71.7 % vs. 49.1 %). There were no important differences between treatments regarding how subjects reported feeling as they fell asleep. Most of the treatment-emergent adverse events with LEM were mild in severity.

Conclusions: Most subjects transitioned successfully to LEM from ZOL (intermittent or frequent use). LEM was well tolerated.

Plain language summary

How does switching insomnia treatment from zolpidem to lemborexant affect patients' sleep?

People with insomnia may need to change their medicine for many different reasons, including the drug not working, side effects, and cost. Lemborexant and zolpidem are two medicines prescribed by doctors for people with insomnia. This study looked at what happened when patients with insomnia who were taking zolpidem wanted a new treatment approach and started taking 5 mg or 10 mg of lemborexant instead.

Abbreviations: AE, adverse event; BMI, body mass index; DORA, dual orexin receptor antagonist; ER, extended release; EXT, Extension (Maintenance) Phase; FAS, Full Analysis Set; IR, immediate release; ISI, Insomnia Severity Index; LEM, lemborexant; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; OSA, obstructive sleep apnea; PGI-I, Patient Global Impression–Insomnia; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event; TRT, Treatment (Titration) Phase; ZOL, zolpidem tartrate; ZOL-ER, zolpidem tartrate extended release; ZOL-IR, zolpidem tartrate immediate release.

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Participants in this study had a 3-week period when they took their usual zolpidem treatment, a 2-week treatment period when they started on lemborexant, and a 12-week extension period when they stayed on lemborexant. Most people who entered the study complained about issues with staying asleep or that zolpidem was not working. For the lemborexant treatment period, participants were divided into three groups based on how often they took zolpidem. They were assigned based on their group to take either 5 mg or 10 mg of lemborexant. Fifty-three participants took part in the study. Overall, 43 of 53 (81 %) participants successfully changed from zolpidem to lemborexant; of these participants, 41 continued lemborexant treatment, and 38 finished the study. At the end of the 2-week initial treatment period, more participants taking lemborexant rather than zolpidem reported that it helped them fall back asleep after waking (71.7 % vs. 49.1 %), and that the severity of their insomnia had decreased. Participants also noted that the feeling of falling asleep was similar with either zolpidem or lemborexant. During LEM treatment, sleepiness and unusual dreams were the most common side effects reported in the higher dose (10 mg) group. This study may help patients and their healthcare providers know what to expect when changing insomnia treatment.

1. Introduction

Patients change insomnia medications for various reasons, including inadequate clinical response, adverse events (AEs), physician/patient preference, or cost [1–4]. However, challenges can arise when transitioning between treatments, particularly between different medication classes [5]. Notably, with the widely prescribed non-benzodiazepine zolpidem tartrate (ZOL) [6], rebound insomnia after abrupt drug discontinuation has been reported [2]. Although benzodiazepine prescribing information [7] and some studies recommend dose tapering of hypnotics [8,9], few clinical studies have assessed the real-world effectiveness of prespecified dose transitioning strategies for insomnia medications.

Lemborexant (LEM) is a competitive dual orexin receptor antagonist (DORA) approved in multiple countries, including the United States, Japan, Canada, Australia, and several Asian and Middle Eastern countries, for the treatment of adults with insomnia. Pivotal phase 3 studies of subjects with insomnia demonstrated a favorable safety profile and improved sleep onset and sleep maintenance through 12 months [10–12] with LEM. Further, no benzodiazepine-like withdrawal symptoms or rebound insomnia were observed with abrupt LEM discontinuation [12].

The current study, E2006-A001-312 (Study 312) assessed prespecified dosing approaches for transitioning subjects from the sedative-hypnotic ZOL to the DORA LEM.

2. Methods

This randomized, open-label, multicenter, phase 3b pilot study was conducted at 15 US sites from July 15, 2019, to June 26, 2020, per the principles of the World Medical Association Declaration of Helsinki. The trial protocol was approved by the appropriate institutional review boards and is registered at ClinicalTrials.gov, identifier NCT04009577. All subjects provided written informed consent before participation.

2.1. Participants

Subjects were ≥18 years of age and met the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition [13] criteria for insomnia disorder. Subjects typically spent ≥7 hours in bed each night [14] and had a history of intermittent (3–4 nights/week) or frequent (≥5 nights/week) ZOL use for ≥1 month, based on the review of drug use data.

Subjects were excluded if they had major sleep disorders other than insomnia or potentially undiagnosed obstructive sleep apnea (OSA) [15], indicated by exclusionary score on screening instruments such as a STOP-Bang score ≥5 (indicating moderate or more severe OSA) [16] or restless legs syndrome (International Restless Legs Scale [17]); took >10 mg ZOL immediate release (ZOL-IR) or >12.5 mg ZOL extended release (ZOL-ER) nightly; used less ZOL than prescribed; reported altering their ZOL tablets; or took habitual daytime naps >3 times/week. Other exclusion criteria included any history of or concomitant medical condition or clinically significant disease that would compromise the subject's ability to safely complete the study; psychotic or unstable recurrent affective disorder(s) within the last ~2 years; suicidal ideation in the last 6 months, or any lifetime suicidal behavior; history of drug or alcohol dependency/abuse within the last 2 years; unwillingness to forgo alcohol consumption within 3 hours of bedtime for the duration of study participation; and females of childbearing potential not currently using a highly effective method of contraception.

2.2. Study design

This study used an open-label design and comprised three phases: Pretreatment, during which all subjects continued their ZOL regiment; Treatment ("TRT"; Titration); and Extension ("EXT"; Maintenance) (Fig. 1).

The Pretreatment Phase consisted of up to a 3-week Screening Period, followed by a 1-day Baseline Period when eligible patients were assigned to a treatment cohort. During the Screening Period subjects recorded frequency and dose of ZOL use for ≥14 (preferably contiguous) days, and for the one-day Baseline Period. Subjects then entered the 2-week TRT and were assigned to a LEM cohort based on frequency of ZOL use. LEM was taken at night within a few minutes of the intention to sleep, per the prescribing information [14].

Cohort 1 (intermittent ZOL use) comprised subjects who took ZOL three or four times during the 2 weeks prior to the Screening Period or who met criteria for intermittent and frequent (≥5 nights/week) ZOL use for 1 week each of the last 2 weeks of the Screening Period. All Cohort 1 subjects began the TRT with LEM 5 mg (LEM5). Subjects decided when to take LEM and were required to take LEM at least once per week during the TRT.

Cohort 2 (frequent ZOL use) included subjects who took ZOL ≥5 nights/week during the last 2 weeks of the Screening Period. Subjects were randomized 1:1 to LEM5 (Cohort 2A) or LEM 10 mg (LEM10; Cohort 2B) and took LEM ≥5 nights/week during the TRT.

Subjects were allowed one LEM dose adjustment during the TRT. All were encouraged, but not required, to remain on their initial LEM dose for 7 days.

Subjects completing the TRT could enter the 12-week EXT where they continued the same LEM dose as they had been taking at the end of the TRT. At any time during the EXT, LEM dose could be titrated up (from LEM5 to LEM10) or down (from LEM10 to LEM5) depending on response and tolerability. Subjects who either completed the entire study or discontinued earlier entered a 4-week Follow-up Period without treatment.

2.3. Assessments

At the start of the Screening Period, subjects completed a Sleep Drug History questionnaire about ZOL and other sleep medication use, chief sleep complaint (difficulty falling asleep, difficulty staying asleep, and/or waking too early), and reason for study participation.

Each morning following a ZOL or LEM dose, subjects completed the Patient Global Impression–Insomnia (PGI-I) [18], which asks whether study medication helped/worsened sleep, decreased/increased time to fall asleep, and increased/decreased total sleep using ratings of 1 (positive), 2 (neutral), and 3 (negative); and appropriateness of study medication strength (ratings: 1 = too strong, 2 = just right, 3 = too weak).

Subjects rated insomnia severity using the Insomnia Severity Index (ISI) [19,20], a 7-item questionnaire evaluating sleep onset and

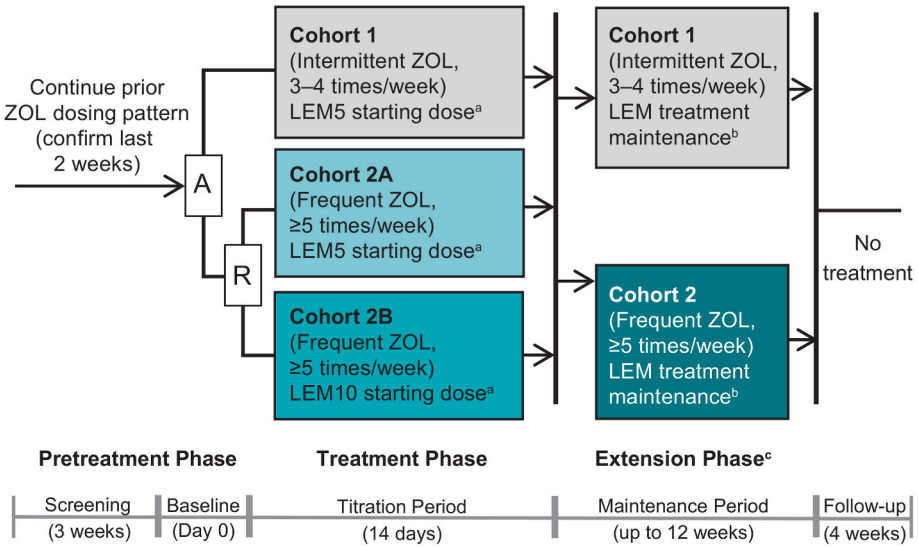

Fig. 1. Study design overview.
[a] Subjects were allowed 1 LEM dose adjustment during the Titration Period.
[b] LEM dose could be titrated up or down during the Extension Phase, depending on response and tolerability.
[c] For those who entered the Extension Phase, the Follow-up Period was 4 weeks after that phase completed. For subjects not entering the Extension Phase, the Follow-up Period started immediately after the end of the Titration Period. Cohort assignment was not changed or reassigned for subjects who chose to enter the Extension Phase.
A, assignment; LEM, lemborexant; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; R, randomization (1:1 ratio); ZOL, zolpidem tartrate.

maintenance and impact on daytime functioning using ratings of 0 (no problem) to 4 (very severe problem) (total score: 22–28 [severe insomnia], 15–21 [moderate insomnia], 8–14 [subthreshold insomnia], 0–7 [no clinically significant insomnia]) [20]. Subjects completed the ISI during the Screening Period and at the end of the TRT.

Subjects rated sleep quality from 1 (extremely poor) to 9 (extremely good) each morning following an evening dose of ZOL/LEM during the Screening Period and TRT.

At the end of the Screening Period and TRT, subjects completed the Sleep Drug Experience Interview regarding whether their medication helped them fall asleep and return to sleep after waking during the night. In the interview, subjects were also asked questions about their subjective experiences. Subjects who discontinued early during the TRT and had unscheduled visits were also interviewed about their experiences with LEM.

Subjects were asked "Did the sleep drug (either ZOL or LEM) help you to fall asleep after taking it?" and "Did the sleep drug (either ZOL or LEM) help you fall back asleep after waking in the middle of the night?" with "Yes" or "No" responses. Subjects who answered "Yes" were then asked, "If the sleep drug (either ZOL or LEM) helped you to fall asleep after taking it, how did you know it was working?" and "If the sleep drug helped you to fall back asleep after waking in the middle of the night, how did you know it was working?" The subjects were presented with a list of 25 possible experiences. For each experience endorsed by the subject, they were asked to rate the intensity of the experience on a scale of 1–5, where 1 indicated low intensity and 5 indicated high intensity. The responses from subjective experience interviews were compared to provide quantitative information on subjects' experiences with ZOL versus LEM.

2.4. Objectives and outcomes

The primary objective of the study was to evaluate the proportion of subjects with insomnia disorder taking ZOL-IR or ZOL-ER, intermittently or frequently, who transition to LEM5 or LEM10, after 2 weeks of receiving LEM. The objectives of the EXT were to assess the longer-term safety and tolerability of a flexible dose of LEM5 or LEM10 taken daily over a period of up to 12 weeks in the subjects who completed the core study.

Other outcomes included sleep medication usage, as measured by dose frequency during the Screening Period and TRT; dose adjustments and time to first dose change during the TRT; end-of-study dose; ratings on each PGI-I item at the end of the Screening Period and TRT; and changes from baseline in ISI score and Quality of Sleep rating at the end of the TRT.

Safety assessments included monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, weight, physical examinations, and suicidal ideation or behavior.

2.5. Statistical analysis

Targeted enrollment was 60 adult subjects (Cohort 1, 20 subjects; Cohort 2, 40 subjects), with sample sizes selected based on study feasibility.

Efficacy analyses were conducted using the Full Analysis Set (FAS; subjects who received ≥1 dose of LEM during the TRT). Safety findings are presented for the Safety Analysis Set (subjects who received ≥1 dose of the study drug and had ≥1 post-dose safety assessment). Evaluations of longer-term safety are presented for the EXT Safety Analysis Set (subjects who received ≥1 dose of the study drug and had ≥1 post-dose safety assessment during the EXT).

Findings from the sleep drug experience questionnaires were summarized descriptively for ZOL and LEM. Percentage values were calculated for those subjects who endorsed that either or both drugs helped them fall asleep or fall back asleep after waking in the night.

3. Results

3.1. Subject disposition and baseline characteristics

Most subjects in the FAS were female (66.0 %) and White (77.4 %); median age was 62.0 years (Table 1).

Per the Sleep History Questionnaire, 40 % and 46.5 % of subjects in Cohorts 1 and 2, respectively, had also used other insomnia treatments as well as ZOL before entering the study. Baseline characteristics of the 43 subjects who entered the EXT were similar to those in the TRT

Table 1
Baseline characteristics (Full Analysis Set, N = 53).

	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2 Frequent ZOL use			Overall (N = 53)
		Cohort 2A (n = 21)	Cohort 2B (n = 22)	Total (n = 43)	
Age, years					
Mean (SD)	62.2 (6.7)	52.7 (13.6)	63.5 (10.4)	58.3 (13.1)	59.0 (12.2)
Median (range)	65.0 (50–70)	56.0 (29–75)	65.0 (38–81)	62.0 (29–81)	62.0 (29–81)
Female, n (%)	7 (70.0)	14 (66.7)	14 (63.6)	28 (65.1)	35 (66.0)
Race, n (%)					
White	8 (80.0)	15 (71.4)	18 (81.8)	33 (76.7)	41 (77.4)
Black or African American	2 (20.0)	5 (23.8)	3 (13.6)	8 (18.6)	10 (18.9)
Asian	0	0	1 (4.5)	1 (2.3)	1 (1.9)
Other	0	1 (4.8)	0	1 (2.3)	1 (1.9)
BMI, mean (SD), kg/m^2	29.8 (5.0)	29.2 (5.6)	28.1 (5.6)	28.6 (5.5)	28.8 (5.4)

BMI, body mass index; SD, standard deviation; ZOL, zolpidem tartrate.

Table 2
Baseline characteristics (Extension Phase – treated subjects).

Characteristic	Cohort 1 Intermittent ZOL use (n = 9)	Cohort 2 Frequent ZOL use			Overall (N = 41)
		Cohort 2A (n = 15)	Cohort 2B (n = 17)	Total (n = 32)	
Age, years					
Mean (SD)	61.8 (6.9)	55.1 (14.1)	61.9 (11.3)	58.8 (12.9)	59.4 (11.9)
Median (range)	64.0 (50–70)	57.0 (29–75)	63.0 (38–81)	62.0 (29–81)	62.0 (29–81)
Female, n (%)	7 (77.8)	12 (80.0)	10 (58.8)	22 (68.8)	29 (70.7)
Race, n (%)					
White	7 (77.8)	12 (80.0)	14 (82.4)	26 (81.3)	33 (80.5)
Black or African American	2 (22.2)	3 (20.0)	2 (11.8)	5 (15.6)	7 (17.1)
Asian	0	0	1 (5.9)	1 (3.1)	1 (2.4)
BMI, mean (SD), kg/m^2	29.6 (5.2)	28.1 (5.0)	28.1 (5.9)	28.1 (5.4)	28.4 (5.3)

BMI, body mass index; SD, standard deviation; ZOL, zolpidem tartrate.

(Table 2).

Of 53 subjects enrolled, 43 (81.1 %) completed the TRT (Fig. 2). Of those who did not complete the TRT, seven of 10 (70 %) discontinued due to AEs (Fig. 2), including two subjects who discontinued due to AEs of intentional overdose (defined as taking more pills than assigned; one receiving LEM5 and one LEM10), one who discontinued LEM5 due to hemiplegia; one subject each who discontinued LEM10 due to sedation complication, paralysis, and diarrhea; and one subject who discontinued LEM10 due to multiple AEs (nausea, sleep paralysis, abnormal dreams, and anxiety).

All 43 subjects completing the TRT continued in the EXT. Of these, 41 received LEM (Cohort 1, n = 9; Cohort 2A, n = 15; Cohort 2B, n = 17; Fig. 2); the remaining two subjects did not receive study treatment. During the EXT, one subject discontinued due to AEs (pneumonia, acute respiratory failure) while receiving LEM10, one discontinued due to inadequate therapeutic effect while receiving LEM5, and one withdrew consent while receiving LEM5 (Fig. 2).

3.2. ZOL usage and treatment experience

At the start of the Screening Period, the mean (SD) duration of ZOL use was 5.6 (2.9) and 4.7 (4.4) years in Cohorts 1 and 2, respectively (Table 3). On the Sleep Drug History questionnaire (Table 3), 92.5 % of subjects reported sleep maintenance problems and 7.5 % reported trouble in falling asleep as primary sleep complaint while using ZOL. Approximately half the subjects in each cohort reported their primary reason for study participation was that ZOL was not working (Table 3).

Among subjects ≥65 years of age, where the maximum recommended ZOL dose is ZOL-IR 5 mg or ZOL-ER 6.25 mg [21], 53.3 % of females (8/15) and 66.7 % of males (4/6) reported using higher-than-recommended doses. Overall, 60.0 % of females (21/35) used a ZOL dose of 10 or 12.5 mg, exceeding the recommended dosage for women [22].

The mean ZOL dose frequency during the Screening Period was 4.3, 6.2, and 6.3 doses per week in Cohorts 1, 2A, and 2B, respectively (Table 4).

3.3. Transition from ZOL to LEM

Overall, 43 of 53 subjects (81.1 %) successfully transitioned to LEM: 9 (90.0 %), 17 (81.0 %), and 17 (77.3 %) in Cohorts 1, 2A, and 2B, respectively. The mean weekly LEM dosing frequency during the TRT was 4.6, 6.0, and 5.6 for Cohorts 1, 2A, and 2B, respectively (Table 4). Among the 41 subjects treated in the EXT, the mean duration of LEM exposure (combined TRT and EXT) was 13.6 weeks (range, 6.0–16.1 weeks); this was similar across cohorts and when analyzed by modal dose.

Six of nine (66.7 %) and nine of 15 (60.0 %) LEM5-treated subjects in Cohort 1 and Cohort 2A, respectively, were up-titrated to LEM10 by the end of the EXT. Median time to first up-titration to LEM10 was 13 days (range, 8–50 days) in Cohort 1 and 16 days (range, 5–38 days) in Cohort 2A. Of those in Cohort 2B, seven of 17 (41.2 %) down-titrated to LEM5 by the end of the EXT; one additional subject in Cohort 2B down-titrated to LEM5 then up-titrated to LEM10 by Day 64. First down-titrations in Cohort 2B most commonly occurred during the first 2 weeks of LEM treatment (range, 2–64 days). At study completion, most subjects (61.0

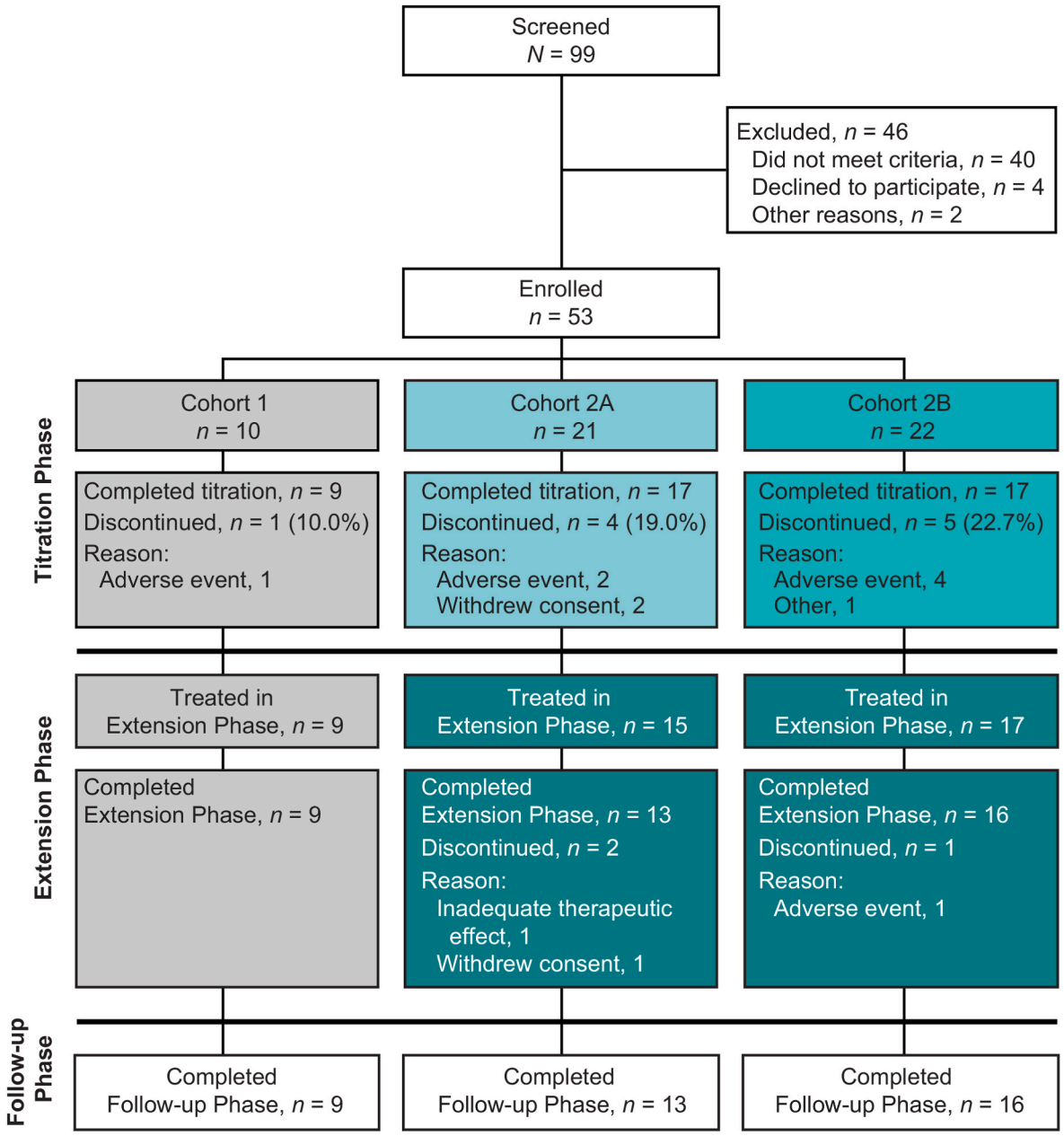

Fig. 2. Subject disposition.

%) were receiving LEM10, including 66.7 % of intermittent and 59.4 % of frequent ZOL users.

3.4. Medication effects (PGI-I)

On the PGI-I, ≥50 % of Cohort 1 and 2B subjects reported positive effects of LEM on sleep and time to fall asleep during the TRT and felt the medication strength was just right (Fig. 3). The proportions of subjects reporting positive effects of LEM on sleep and time to fall asleep in Cohorts 1 and 2B were numerically greater at the end of the TRT than at the end of the Screening Period (Fig. 3).

In Cohort 2A, approximately one-third to half of subjects reported positive effects of LEM on all items of the PGI-I, which was lower than reported with ZOL (Fig. 3). A numerically higher proportion of subjects reported a positive effect on time to fall asleep after receiving LEM5 or LEM10 than after ZOL, while proportions of subjects reporting positive effects on sleep and total sleep time were similar across drugs/doses.

LEM medication strength was considered "just right" at the end of the TRT for 80.0 %, 38.1 %, and 50.0 % of subjects in Cohorts 1, 2A, and 2B, respectively (Fig. 3d), whereas 20.0 %, 61.9 %, and 36.4 % of subjects, respectively, reported their LEM medication strength as "too weak." By drug/dose, medication strength was considered "just right" by 54.7 % of subjects with ZOL at the end of the Screening Period and by 61.9 % and 43.8 % for LEM5 and LEM10, respectively, at the end of titration.

3.5. Insomnia Severity Index

Mean ISI score decreased from 14.1 at the end of the Screening Period to 9.5 at end of the TRT (mean [SD] improvement of −4.6 [6.3]); improvements in mean ISI score were seen in each cohort (Table 5).

3.6. Quality of Sleep Rating

The mean (SD) Quality of Sleep Rating score was 5.3 (1.5) and 5.1

Table 3
ZOL history (Full Analysis Set, N = 53) and Sleep Drug History Questionnaire (Safety Analysis Set, N = 53).

	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2 Frequent ZOL use			Overall (N = 53)
		Cohort 2A (n = 21)	Cohort 2B (n = 22)	Total (n = 43)	
ZOL history					
Dose, n (%)					
ZOL-IR 5 mg	3	6	7	13	16
	(30.0)	(28.6)	(31.8)	(30.2)	(30.2)
ZOL-IR 10 mg	7	15	14	29	36
	(70.0)	(71.4)	(63.6)	(67.4)	(67.9)
ZOL-ER 6.25 mg	0	0	1 (4.5)	1 (2.3)	1 (1.9)
ZOL-ER 12.5 mg	0	4 (19.0)	1 (4.5)	5 (11.6)	5 (9.4)
Other dose strengths	0	1 (4.8)	0	1 (2.3)	1 (1.9)
Duration of use, years					
N	10	19	20	39	49
Mean (SD)	5.6 (2.9)	4.5 (5.2)	4.9 (3.6)	4.7 (4.4)	4.9 (4.2)
Median	5.5	2.5	4.8	3.4	4.4
Min, max	0.2, 10.2	0.1, 20.4	0.05, 11.2	0.05, 20.4	0.05, 20.4
Chief complaint, n (%)					
What bothers you about your sleep now?[a]					
Difficulty falling asleep	1 (10.0)	2 (9.5)	1 (4.5)	3 (7.0)	4 (7.5)
Difficulty staying asleep	4	6	4	10	14
	(40.0)	(28.6)	(18.2)	(23.3)	(26.4)
Waking too early	5	13	17	30	35
	(50.0)	(61.9)	(77.3)	(69.8)	(66.0)
Why are you interested in participating in this study?[a]					
ZOL is not working	5	11	11	22	27
	(50.0)	(52.4)	(50.0)	(51.2)	(50.9)
Concerns about taking ZOL	2	3	5	8	10
	(20.0)	(14.3)	(22.7)	(18.6)	(18.9)
Residual daytime sleepiness	0	2 (9.5)	0	2 (4.7)	2 (3.8)
ZOL side effects	0	0	2 (9.1)	2 (4.7)	2 (3.8)
Doctor recommendation	0	1 (4.8)	0	1 (2.3)	1 (1.9)
Other	3	4	4	8	11
	(30.0)	(19.0)	(18.2)	(18.6)	(20.8)
Have you previously taken sleep drugs other than ZOL?[a]					
Yes	4	7	13	20	24
	(40.0)	(33.3)	(59.1)	(46.5)	(45.3)
No	6	14	9	23	29 (54.7)
	(60.0)	(66.7)	(40.9)	(53.5)	

SD, standard deviation; ZOL, zolpidem tartrate; ZOL-ER, zolpidem tartrate extended release; ZOL-IR, zolpidem tartrate immediate release.
[a] Subjects could select one response per question.

Table 4
Dosing frequency[a] (Safety Analysis Set, N = 53).

	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2 Frequent ZOL use			Overall (N = 53)
		Cohort 2A (n = 21)	Cohort 2B (n = 22)	Total (n = 43)	
ZOL doses taken per week during the Screening Period					
Mean (SD)	4.3 (0.6)	6.2 (0.8)	6.3 (0.7)	6.2 (0.7)	5.9 (1.0)
Median	4.4	6.3	6.5	6.4	6.1
Min, max	3.3, 5.2	4.1, 7.0	4.7, 7.0	4.1, 7.0	3.3, 7.0
LEM doses taken per week during the Titration Period					
Mean (SD)	4.6 (1.7)	6.0 (1.0)	5.6 (1.5)	5.8 (1.3)	5.6 (1.5)
Median	4.2	6.5	6.2	6.5	6.2
Min, max	2.0, 7.0	3.7, 7.0	0.5, 7.0[b]	0.5, 7.0[b]	0.5, 7.0[b]

LEM, lemborexant; SD, standard deviation; ZOL, zolpidem tartrate.
[a] (Number of doses taken/duration) × 7.
[b] The minimum LEM dosing frequency of 0.5 doses per week is due to one subject who took one dose over 2 weeks before early discontinuation.

(1.7) at the end of the ZOL treatment and the TRT, respectively. Mean scores were consistent across cohorts (data not shown).

3.7. Sleep Drug Experience Interview

All 53 subjects (10 in Cohort 1, 43 in Cohort 2) answered both Sleep Drug Experience Interview question sets, which addressed (1) Experiences endorsed by subjects reporting that ZOL or LEM helped them fall asleep after taking that drug (Supplemental Table 1; and (2) Experiences endorsed by subjects reporting that ZOL or LEM helped them fall back asleep after waking in the middle of the night (Supplemental Table 2). These Sleep Drug Experience Interview question sets were administered after subjects took either ZOL or LEM after the Pretreatment Phase. All 53 subjects answered both Sleep Drug Experience interview questions with respect to ZOL after the Pretreatment Phase comprising 10 subjects in Cohort 1 and 43 subjects in Cohort 2. In the TRT, 51 of 53 subjects (96.2 %) answered the questions with respect to LEM, comprising 10 subjects in Cohort 1 and 41 subjects in Cohort 2. Across both cohorts, 19 of 21 subjects (90.5 %) taking LEM5 as a last dose and all 32 subjects taking LEM10 as a last dose answered the questions.

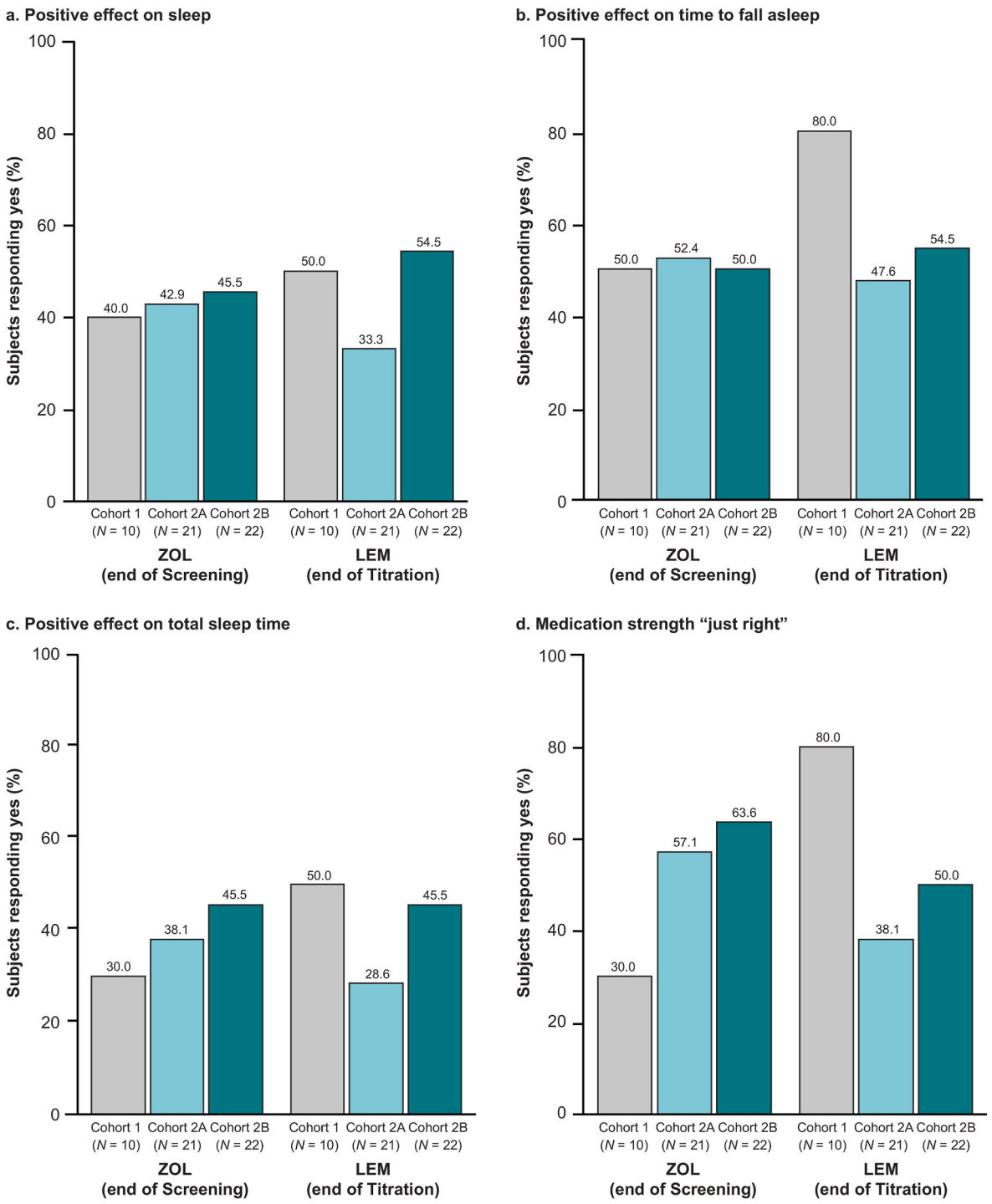

Fig. 3. Proportions of subjects reporting positive PGI-I scores (Full Analysis Set). Findings are reported for ZOL at end of the Screening Period and for LEM. LEM, lemborexant; PGI-I, Patient Global Impression–Insomnia; ZOL, zolpidem tartrate.

3.7.1. Falling asleep

In the Pretreatment Phase, 48 subjects (90.6 %) reported that ZOL helped them fall asleep, including all subjects in Cohort 1 and 38 subjects (88.4 %) in Cohort 2. In the TRT, 45 subjects (84.9 %) reported that LEM helped them fall asleep, including all 10 subjects in Cohort 1 and 35 subjects (81.4 %) in Cohort 2. Across both cohorts, 16 subjects (76.2 %) whose last dose was LEM5 and 29 subjects (90.6 %) whose last dose was LEM10 reported that LEM helped them fall asleep (Table 6).

The most frequently endorsed experiences (>75 %) with respect to falling asleep were "feeling relaxed/calm," (with ZOL 42/48 = 87.5 %; with LEM 40/45 = 88.9 %) "drowsiness, grogginess, sleepiness," (with ZOL 37/48 = 77.1 %; with LEM 38/45 = 84.4 %) and "dreams," (with ZOL 38/48 = 79.2 %; with LEM 36/45 = 80.0: Supplemental Table 1).

3.7.2. Falling back asleep after waking in the middle of the night

Twenty-six subjects (49.1 %) reported that ZOL helped them fall back asleep after waking in the night, including four subjects (40.0 %) in Cohort 1 and 22 subjects (51.2 %) in Cohort 2. In contrast, 38 subjects (71.7 %) reported that LEM helped them fall back asleep (Table 6).

As with the types of experiences endorsed, the proportions of subjects

Table 5
Change from baseline in Insomnia Sleep Index (Full Analysis Set, N = 53).

	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2 Frequent ZOL use			Overall (N = 53)
		Cohort 2A (n = 21)	Cohort 2B (n = 22)	Total (n = 43)	
Baseline (end of Pretreatment Phase on ZOL treatment)					
Mean (SD)	18.0 (4.0)	14.2 (6.0)	12.3 (6.1)	13.2 (6.1)	14.1 (6.0)
Min, max	13, 24	2, 27	2, 24	2, 27	2, 27
End of Treatment Phase on LEM treatment					
Mean (SD)	10.9 (6.7)	9.7 (6.3)	8.7 (5.4)	9.2 (5.8)	9.5 (5.9)
Min, max	0, 19	2, 23	0, 20	0, 23	0, 23
Change from baseline					
Mean (SD)	−7.1 (8.1)	−4.5 (6.3)	−3.5 (5.2)	−4.0 (5.7)	−4.6 (6.3)
Min, max	−21, 1	−14, 15	−14, 9	−14, 15	−21, 15

LEM, lemborexant; SD, standard deviation; ZOL, zolpidem tartrate.

Table 6
Sleep drug experience (Full Analysis Set, N = 53).

	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2 Frequent ZOL use			Overall (N = 53)
		Cohort 2A (n = 21)	Cohort 2B (n = 22)	Total (n = 43)	
Helped me sleep[a]					
ZOL	10 (100)	18 (85.7)	20 (90.9)	38 (88.4)	48 (90.6)
LEM	10 (100)	16 (76.2)	19 (86.4)	35 (81.4)	45 (84.9)
Helped me fall back asleep[b]					
ZOL	4 (40.0)	9 (42.9)	13 (59.1)	22 (51.2)	26 (49.1)
LEM	8 (80.0)	15 (71.4)	15 (68.2)	30 (69.8)	38 (71.7)

All values are n (%).
LEM, lemborexant; ZOL, zolpidem tartrate.
[a] Subject responded "Yes" to item: "Did ZOL/LEM help you fall asleep after taking it?"
[b] Subject responded "Yes" to item: "Did ZOL/LEM help you fall back asleep after waking in the middle of the night?"

Table 7
Overview of TEAEs during the Treatment Phase[a] and Extension Phase[b].

Subjects with ≥1 TEAE, n (%)	By cohort				On-treatment dose	
	Cohort 1 Intermittent ZOL use (n = 10)	Cohort 2A Frequent ZOL use (n = 21)	Cohort 2B Frequent ZOL use (n = 22)	Cohort 2 total (n = 43)	LEM5 (n = 36)	LEM10 (n = 37)
Treatment Phase						
Any TEAE	4 (40.0)	5 (23.8)	11 (50.0)	16 (37.2)	5 (13.9)	15 (40.5)
TEAEs in ≥2 subjects in any group, n (%)						
Abnormal dreams	0	0	4 (18.2)	4 (9.3)	0	4 (10.8)
Somnolence	0	1 (4.8)	3 (13.6)	4 (9.3)	1 (2.8)	3 (8.1)
Accidental overdose	0	2 (9.5)	0	2 (4.7)	2 (5.6)	0
Extension Phase						
Any TEAEs	4 (44.4)	4 (26.7)	10 (58.8)	14 (43.8)	5 (15.6)	14 (37.8)
Treatment related[c]	0	2 (13.3)	7 (41.2)	9 (28.1)	0	9 (24.3)
Severe	0	0	2 (11.8)	2 (6.3)	0	2 (5.4)
TEAEs leading to study drug discontinuation	0	0	1 (5.9)	1 (3.1)	0	1 (2.7)
TEAEs associated with misuse	1 (11.1)	0	0	0	1 (3.1)	0
SAEs	0	0	1 (5.9)	1 (3.1)	0	1 (2.7)
Deaths	0	0	0	0	0	0
TEAEs in ≥2 subjects in any group, n (%)						
Somnolence	0	0	3 (17.6)	3 (9.4)	0	3 (8.1)
Abnormal dreams	0	0	2 (11.8)	2 (6.3)	0	2 (5.4)
Urinary tract infection	0	1 (6.7)	1 (5.9)	2 (6.3)	1 (3.1)	1 (2.7)

LEM, lemborexant; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; SAE, serious adverse event; TEAE, treatment-emergent adverse event (defined as an adverse event that started on or after the date of first dose of study drug, up to 14 days after the last dose of study drug); ZOL, zolpidem tartrate.
[a] Treatment Phase Safety Analysis Set, N = 53.
[b] Extension Phase Safety Analysis Set, N = 41.
[c] Includes TEAEs considered by the investigator to be related to study drug or TEAEs with missing causality.

endorsing each experience were similar between LEM and ZOL (Supplemental Table 2). The most frequently endorsed experiences (>75 %) with respect to falling asleep were "feeling relaxed/calm," (with ZOL 23/26 = 88.5 %; with LEM 30/38 = 78.9 %) "drowsiness, grogginess, sleepiness," (with ZOL 20/26 = 76.9 %; with LEM 26/38 = 68.4 %), "dreams," (with ZOL 22/26 = 84.6 %; with LEM 24/38 = 63.2 %) and "peaceful," (with ZOL 22/26 = 84.6 %; with LEM 30/38 = 78.9 %; Supplemental Table 2).

Cohort did not appear to impact the results. Experiences endorsed with LEM were similar between subjects taking LEM5 and LEM10 as their last doses.

3.8. Safety

TEAEs occurred more frequently with LEM10 compared with LEM5; most were mild (45 %) or moderate (45 %) in severity (Table 7). The most common TEAEs were somnolence (n = 4) and abnormal dreams (n

= 4) in the TRT and somnolence (n = 3) in the EXT.

There were no serious TEAEs during the TRT. During the EXT, one LEM10-treated subject discontinued due to serious AEs (pneumonia, acute respiratory failure, pulmonary embolism) not considered related to study treatment; the subject tested positive for COVID-19.

No TEAEs were suggestive of rebound insomnia or withdrawal effects following ZOL discontinuation. Overdose (taking >1 tablet per night) was reported by one LEM10-treated subject in Cohort 1 and by three LEM5-treated subjects in Cohort 2A during the TRT (two accidental, two intentional, but not associated with suicidal ideation; Table 7).

4. Discussion

In this open-label study, >80 % of subjects successfully transitioned from ZOL to LEM and chose to continue their LEM treatment into the EXT. These new data supplement existing knowledge about the efficacy and safety profile of LEM and may inform clinicians and patients about what subjective experiences may be associated with transitioning from ZOL to LEM.

Before transition, subjects took ZOL-IR or ZOL-ER intermittently or frequently, reflecting real-world use. Notably, more than half of subjects ≥65 years of age and female subjects reported taking a higher dosage strength of ZOL than specified in the prescribing instructions, suggesting insufficient efficacy and/or tolerance. Most subjects' primary reason for wanting to transition to LEM was their perception that ZOL was not working, with their chief complaint being problems with sleep maintenance. Additionally, almost half of subjects reported taking other insomnia medications besides ZOL before the study, suggesting these subjects may not have experienced sufficient relief with previous treatments.

The majority of subjects reported that ZOL and LEM helped them fall asleep, and more subjects taking LEM in the TRT than those taking ZOL in the Screening Period reported that the drug helped them fall back asleep after waking. At the study start, many subjects complained of waking too early or having difficulty staying asleep while taking ZOL, which is reflected by fewer subjects reporting that ZOL helped them fall back asleep compared with LEM. Most subjects (n = 52) had been taking ZOL-IR, compared with only six subjects taking ZOL-ER. In the United States, ZOL-IR is indicated for sleep initiation but not sleep maintenance [4], which could explain why a large proportion of subjects complained of waking too early or difficulties staying asleep with ZOL at the start of the study, and why only around half of the subjects reported ZOL helping them fall back asleep after waking. Transitioning to LEM from ZOL reduced sleep maintenance problems for many patients in this study, with more patients reporting that LEM helped them return to sleep after waking. Scores on the PGI-I and the ISI also reflected improvement with LEM, with the latter showing a mean decrease of 4.6 points within 2 weeks.

These findings are consistent with previous studies comparing LEM with ZOL. For example, in a phase 3 trial of patients ≥55 years of age with insomnia, LEM treatment led to greater improvements in sleep onset and maintenance versus ZOL-ER and was effective in decreasing awakening after sleep onset in the latter half of the night [11]. In a phase 1 trial of healthy subjects ≥55 years of age who were awakened in the middle of the night 4 hours after LEM10 dosing, subjects returned to sleep significantly faster than those who received ZOL-ER [23].

Although subjects in the current study could decide which nights to take LEM, the mean number of weekly doses did not increase after transitioning from ZOL to LEM. Approximately three-quarters of subjects required LEM dose adjustments, with >60 % starting on LEM5 and increasing to LEM10, whereas 39 % remained on or reduced to LEM5 by the study end.

On the PGI-I, subjects in Cohort 2A were less likely to report positive sleep effects with LEM. However, PGI-I assessments were conducted during the TRT and may reflect a need for a higher dose, as shown by the proportion of subjects who up-titrated to LEM10. Supporting this, subjects in Cohort 2A were more likely than subjects in Cohorts 1 and 2B to report that LEM medication strength was too weak. Early up-titration to LEM10 may be required for frequent ZOL users to achieve a satisfactory response.

In the Sleep Experience Interview, the most common subjective experience in these subjects was feeling calm and relaxed while falling asleep and after waking in the middle of the night, for both ZOL and LEM. Subjects who were intermittent ZOL users generally had similar subjective experiences to those who were frequent ZOL users. Overall, the most common subjective experiences endorsed were pleasant in nature (e.g., "relaxed"/"calm", peaceful) and the more negative experiences were relatively infrequent (e.g., depressed, frightened). Rapid onset of sleep has been identified as a key desirable subjective experience in sleep medication [24], and a relatively high proportion of subjects experienced "falling asleep quickly" with both ZOL and LEM in this study. This analysis shows that the most frequently endorsed sleep-onset and sleep-maintenance experiences were similar between ZOL and LEM.

The safety profile for subjects transitioning from ZOL to LEM was consistent with the known safety profile of LEM, and observed TEAEs were consistent with the safety profile of LEM in phase 3 trials [11,12]. Similar to this study, TEAEs reported in two phase 3 studies were mostly mild/moderate in severity, with somnolence, headache, and nasopharyngitis most commonly reported [10,11]. LEM was generally well tolerated in this study.

A recent retrospective analysis from Japan reported that 80 of 137 patients given the opportunity to transition from benzodiazepine hypnotics to LEM did so successfully (average dose, 6.2 mg), while 57 continued on benzodiazepines [25]. The group that successfully transitioned to LEM had a shorter mean duration of disease and shorter administration period of benzodiazepines (or hypnotic diazepam equivalent) compared with the group remaining on benzodiazepines. These findings align with the present study in demonstrating that many patients can directly transition from another drug class to LEM therapy.

5. Conclusion

This open-label study used a real-world design to understand dose transition in patients receiving individualized ZOL regimens who wanted to change insomnia medications. Subjects were randomized to LEM depending on the previous ZOL dose. They were encouraged to try their initial dose assignment during the first week before making dose adjustment, simulating likely guidance in clinical practice.

This approach provides important preliminary data to facilitate discussions of transitioning to LEM for patients not satisfied with ZOL. However, these findings may not be generalizable to patients wanting to switch to LEM but satisfied with their current medication, or to those advised by their physician to change medications for other reasons.

Similar proportions of subjects reported that ZOL and LEM helped them fall asleep; but more subjects taking LEM, compared with ZOL, reported that it helped them fall back asleep after waking in the middle of the night.

Subjective experiences endorsed by subjects while falling asleep and falling back asleep in the middle of the night were generally similar between ZOL and LEM. However, greater than 10 % more subjects endorsed the experiences as "peaceful" with LEM compared with ZOL, and approximately 10 % fewer subjects endorsed the experience "difficulty with remembering details of the night right before falling asleep" with LEM versus ZOL. Over 20 % of subjects reported improvement in sleep maintenance with LEM. Among the subjects who were able to fall back asleep in the middle of the night with ZOL or LEM, fewer subjects (>10 %) endorsed the experience of "dreams," "feeling drugged," "weakness," or "numbness" with LEM. The number of subjects who endorsed "falling asleep so quickly that you don't remember falling asleep" were higher with ZOL. Overall, these results suggest a similar or better overall experience for patients transitioning from ZOL to LEM for

improvement in sleep maintenance or other issues. These observations may aid discussions with patients around what experiences to expect when considering a transition to LEM.

These are the first findings that show a successful next-dose transitioning from the sedative-hypnotic ZOL to a drug in a different insomnia medication class and provide a practical demonstration of transitioning patients from ZOL to LEM relevant to primary care practice. Following 2 weeks of LEM treatment, most subjects transitioned directly from intermittent or frequent ZOL use to LEM. The safety profile for subjects transitioning from ZOL to LEM was consistent with the phase 3 LEM clinical program. Finally, based on clinical response and tolerability, this study supports the recommended starting dose of LEM5 with the consideration of increasing to LEM10.

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Data availability

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

CRediT authorship contribution statement

Maha Ahmad: Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **James Kelly:** Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **C. Brendan Montano:** Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Dinesh Kumar:** Data curation, Formal analysis, Funding acquisition, Methodology, Validation, Writing – original draft, Writing – review & editing. **Carlos Perdomo:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Manoj Malhotra:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jess Amchin:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Margaret Moline:** Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

J. Kelly is an employee of Clinilabs Drug Development Corporation and M. Ahmad was an employee of Clinilabs Drug Development Corporation at the time of the study. Clinilabs Drug Development Corporation received grants from Eisai Inc. during the conduct of the study. C. B. Montano is an employee of CT Clinical Research, D. Kumar, C. Perdomo and M. Moline are employees of Eisai Inc. M. Malhotra and J. Amchin were employees of Eisai Inc. at the time of the study. This study was sponsored by Eisai Inc., manufacturer/licensee of LEM. Eisai Inc. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

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Appendix A. Supplementary data

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