pii: jc-17-00052 http://dx.doi.org/10.5664/jcsm.6800

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Lemborexant, A Dual Orexin Receptor Antagonist (DORA) for the Treatment of Insomnia Disorder: Results From a Bayesian, Adaptive, Randomized, Double-Blind, Placebo-Controlled Study

Patricia Murphy, PhD[1]; Margaret Moline, PhD[1]; David Mayleben, PhD[2]; Russell Rosenberg, PhD[3]; Gary Zammit, PhD[4]; Kate Pinner, MSc[5]; Shobha Dhadda, PhD[1]; Quan Hong, PhD[1]; Luigi Giorgi, MD[5]; Andrew Satlin, MD[1]

[1]Eisai Inc, Woodcliff Lake, New Jersey; [2]Community Research Inc, Cincinnati, Ohio; [3]NeuroTrials Research Inc, Atlanta, Georgia; [4]CLINILABS, Inc, New York, New York; [5]Eisai Ltd, Hatfield, United Kingdom

Study Objectives: To identify dose(s) of lemborexant that maximize insomnia treatment efficacy while minimizing next-morning residual sleepiness and evaluate lemborexant effects on polysomnography (PSG) measures (sleep efficiency [SE], latency to persistent sleep [LPS], and wake after sleep onset [WASO]) at the beginning and end of treatment.

Methods: Adults and elderly subjects with insomnia disorder per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition were enrolled in a multicenter, randomized, double-blind, placebo-controlled, Bayesian, adaptive, parallel-group study, receiving lemborexant (1, 2.5, 5, 10, 15, 25 mg) or placebo for 15 nights. Efficacy assessments included a utility function that combined efficacy (SE) and safety (residual morning sleepiness as measured by Karolinska Sleepiness Scale [KSS]), PSG measures, and sleep diary. Safety assessments included KSS, Digit Symbol Substitution Test, computerized reaction time tests, and adverse events (AEs).

Results: A total of 616 subjects were screened; 291 were randomized. Baseline characteristics were similar between lemborexant groups and placebo (~63% female, median age: 49.0 years). The study was stopped for early success after the fifth interim analysis when the 15-mg dose met utility index/KSS criteria for success; 3 other doses also met the criteria. Compared with placebo, subjects showed significant improvements in SE, subjective SE, LPS, and subjective sleep onset latency at the beginning and end of treatment for lemborexant doses ≥ 5 mg ($P < .05$). WASO and subjective WASO showed numerically greater improvements for doses > 1 mg. AEs, mostly mild to moderate, included dose-related somnolence.

Conclusions: Lemborexant doses ranging from 2.5–10 mg provided efficacy for the treatment of insomnia while minimizing next-morning residual sleepiness.

Clinical Trial Registration: Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Bayesian Adaptive Randomization Design, Dose Response Study of the Efficacy of E2006 in Adults and Elderly Subjects With Chronic Insomnia; URL: https://clinicaltrials.gov/ct2/show/NCT01995838; Identifier: NCT01995838

Keywords: Bayesian method, insomnia, orexin receptor antagonists

Citation: Murphy P, Moline M, Mayleben D, Rosenberg R, Zammit G, Pinner K, Dhadda S, Hong Q, Giorgi L, Satlin A. Lemborexant, a dual orexin receptor antagonist (DORA) for the treatment of insomnia disorder: results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. *J Clin Sleep Med.* 2017;13(11):1289–1299.

INTRODUCTION

Insomnia is highly prevalent, with approximately 30% of the general population reporting symptoms of insomnia[1] and 6.6% satisfying the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[2] criteria for insomnia disorder.[3] Non-depressed individuals with insomnia are twice as likely to develop depression compared with individuals not suffering from insomnia.[4] Insomnia results in lost work performance amounting to an estimated $63 billion annually.[5]

Benzodiazepines, nonbenzodiazepine hypnotics ("z-drugs" such as zolpidem, zolpidem CR, and eszopiclone), and sedating antidepressants are the primary prescription medications currently used to treat insomnia in the United States, but there is need for agents that more effectively reduce wakefulness throughout the night without safety issues such as complex sleep-related behaviors and cognitive/psychomotor impairments.[6–11] Impairment of driving abilities the day following therapy and falls by the elderly are also key safety issues that have come to the forefront with benzodiazepines and z-drugs.[10–13] These agents also may lose efficacy over time.[9,14] These issues with currently available therapies have driven interest in the orexin system as a different target for developing

BRIEF SUMMARY

Current Knowledge/Study Rationale: There is a need for improved efficacy and safety of prescription medications used for treating insomnia. In particular, patients would benefit if treatments showed greater efficacy in reducing wakefulness throughout the night without producing important residual morning sleepiness.

Study Impact: This study of lemborexant, a dual orexin receptor antagonist in clinical development, identified doses that showed promising activity for treatment of insomnia, while not substantially affecting either subjective or objective measures of residual morning sleepiness. These lemborexant doses will be evaluated in additional clinical trials.

insomnia drugs. Orexins are neuropeptides involved with regulating the sleep-wake cycle[15]; they help promote wakefulness by binding to the G-protein–coupled receptors, OX1R and OX2R.[9,16] The dual orexin receptor antagonist (DORA) suvorexant (approved in the United States and Japan[17]) has been shown to treat insomnia disorder and is thought to block the wakefulness that is interfering with sleep.[16] However, higher doses have been associated with residual daytime sleepiness, which is a safety concern.[18]

Lemborexant (E2006) is an orally active investigational DORA in clinical development. Presented here are the results from a phase 2 study of the efficacy and safety of lemborexant in the treatment of subjects with insomnia disorder. The study used a Bayesian adaptive design to permit more efficient use of the data. Frequent interim analyses (IAs) utilized emerging on-treatment outcomes to adjust randomization ratios to assign more subjects to the most successful doses and to test for early signals of success or futility. Both approaches improved the efficiency of the study design for dose selection and decision-making.

METHODS

Objectives

The primary study objective was to identify the dose or doses of lemborexant that maximized efficacy for the treatment of insomnia while minimizing next-morning residual sleepiness. This objective was evaluated using a utility function of efficacy and safety that combined sleep efficiency (SE) ([total sleep time / time in bed] × 100%) as measured by polysomnography (PSG) with residual morning sleepiness as rated on the Karolinska Sleepiness Scale (KSS). Because the primary objective focused on identifying a dose or doses that balanced efficacy and safety, it was necessary to find a means of jointly assessing both factors. To do this, a utility function integrating SE and KSS was developed. SE was used in the utility function because it takes into account both sleep onset and sleep maintenance in one parsimonious measure. The KSS was included as a validated measure of subjective sleepiness that has been found to be sensitive to sleepiness in other studies of treatments for insomnia.[19] Utility indices combining efficacy and safety variables have also been developed and used effectively in studying treatments in other disease areas.[20]

Clinically significant differences from placebo were defined in advance as superiority by ≥ 6% (equivalent to > 30 minutes increase in time spent asleep, which is a clinically significant difference) on change from baseline of SE at days 1 and 2 and no change of > 4 units from baseline on the KSS at 1 hour after morning waketime on days 2 and 3. Using this definition, a score of zero on the utility function corresponded to either insufficient efficacy or unacceptable next-day sleepiness. A utility function score > 1 represented a sufficiently positive benefit:risk ratio to warrant the selection of doses for further study. This utility function was the first primary endpoint of the study. A second primary endpoint was a change of > 4 units relative to placebo on the KSS at 1 hour after waketime on days 15 and 16, included as a measure of unacceptable safety after 15 days of treatment. Thus, at any IA, randomization could be stopped for an early signal of success if the Bayesian analysis indicated there was at least 1 dose with at least an 85% probability of having a utility function > 1, and if that dose did not meet the operational definition of unacceptable safety at days 15 and 16. If randomization was not stopped early, success at study completion was defined similarly, except that the probability of the utility function > 1 was only required to be at least 80%.

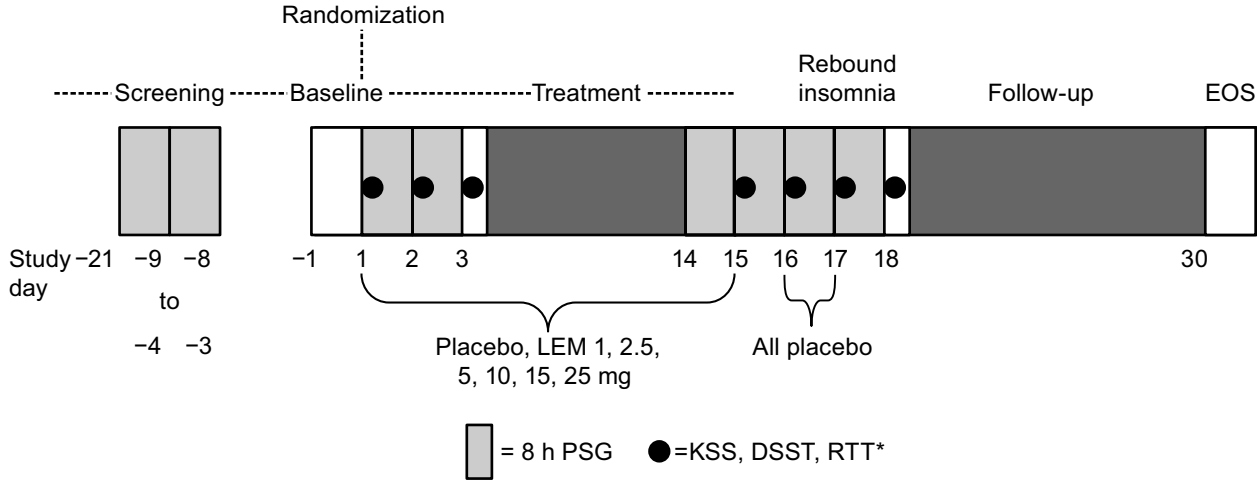
Secondary objectives were evaluated by additional PSG measures of sleep improvement comparing each dose of lemborexant with placebo. Efficacy at the beginning of treatment was measured as change from mean at baseline to mean after dosing on day 1 and day 2 for SE (overall efficacy), latency to persistent sleep (LPS; sleep onset, defined as minutes from "lights off" to the first epoch of 20 consecutive epochs of nonwakefulness), and wake after sleep onset (WASO; sleep maintenance, defined as minutes of wakefulness from the onset of persistent sleep until "lights on"). Efficacy at the end of treatment was measured as change in SE, LPS, and WASO from mean baseline to mean after dosing on days 14 and 15. Potential durability of effect from the beginning to end of treatment was evaluated as change from baseline in mean SE, LPS, and WASO after the first 2 doses compared with change from baseline in mean SE, LPS, and WASO after the last 2 doses. Potential for rebound insomnia was measured as change from mean SE at baseline to mean SE after dosing (with placebo washout) on days 16 and 17.

Exploratory efficacy objectives included subject-reported outcomes on the sleep diary. Subjects completed sleep diaries on each morning of the study, providing self-reported assessments of sleep including subjective sleep efficiency (sSE; [subjective total sleep time / subjective time in bed] × 100%), subjective sleep onset latency (sSOL; estimated minutes from lights off to sleep onset), and subjective wakefulness after sleep onset (sWASO; estimated minutes of wakefulness during the night after initial sleep onset).

Study Population

Study participants were men and women 19 to 80 years of age who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[21] criteria for insomnia disorder. Subjects were also required to meet the following objective inclusion criteria on 2 consecutive screening/baseline PSGs: LPS average of ≥ 30 minutes with neither night < 15 minutes; and/or WASO average of ≥ 30 minutes with neither night < 20 minutes; and an SE average of ≤ 85% with neither night > 87.5%. At the first screening visit, an in-depth interview with the investigator visit included self-reported sleep, medical, and psychiatric history. In addition, medical records were reviewed if available. Questionnaires were administered to rule out subjects with lifetime suicidal behavior, suicidality within the past 6 months, or threshold levels of self-reported depression and anxiety symptoms. Urine samples were tested for common drugs of use/abuse (eg, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, amphetamines, and methamphetamine). Subjects with diagnosis of a sleep disorder other than insomnia were excluded. Use of sleep medication or concomitant medications to treat insomnia

Figure 1—Study design.



* = assessed within 15 minutes, and at 1 hour and 2 hours after morning waketime. DSST = Digit Symbol Substitution Test, EOS = end of study, KSS = Karolinska Sleepiness Scale, LEM = lemborexant, PSG = polysomnography, RTT = Reaction Time Task.

symptoms within 2 weeks of first screening/baseline PSG, or having a current diagnosis or being treated for major medical or psychiatric disorders excluded subjects from this study.

Written informed consent was obtained from all subjects after they received an explanation of study procedures, risks, and benefits. The study protocol was approved by the relevant institutional review board and was conducted in accordance with principles of Good Clinical Practice and any applicable local regulations.

Study Design and Procedure

The study was conducted at 22 investigational sites in the United States from November 13, 2013 to April 29, 2014 (ClinicalTrials.gov NCT01995838). Study treatment was administered for 15 days, followed by a single-blind placebo washout for 2 days (**Figure 1**). The study drug was taken 30 minutes before a subject's median habitual bedtime when in clinic and 30 minutes before self-selected bedtime when at home. Subjects continued to complete the sleep diary for 12 additional days after the treatment period.

A Bayesian dose-response adaptive design with response adaptive randomization (RAR) was used to fully explore the dose-response curve of lemborexant. The RAR utilized results from frequent IAs to update randomization ratios and randomize subjects to placebo or to 1 of 6 active lemborexant doses (1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, or 25 mg per day) by weighting the allocation toward the doses most likely to meet prespecified efficacy and safety criteria according to the utility function that combined the evaluation of efficacy as measured by SE and next-morning residual sleepiness as measured by the KSS. The first 105 subjects were randomized at a fixed 1:1:1:1:1:1:1 ratio to placebo or to 1 of the active lemborexant dose arms. After 15 subjects were allocated to each group, the first IA was conducted, and RAR was started. A maximum sample size of 300 subjects was set. An independent data monitoring committee conducted the IA every 2 weeks. After each IA, the study could be stopped for success or futility, or continued with updated randomization allocations.

Safety Assessments

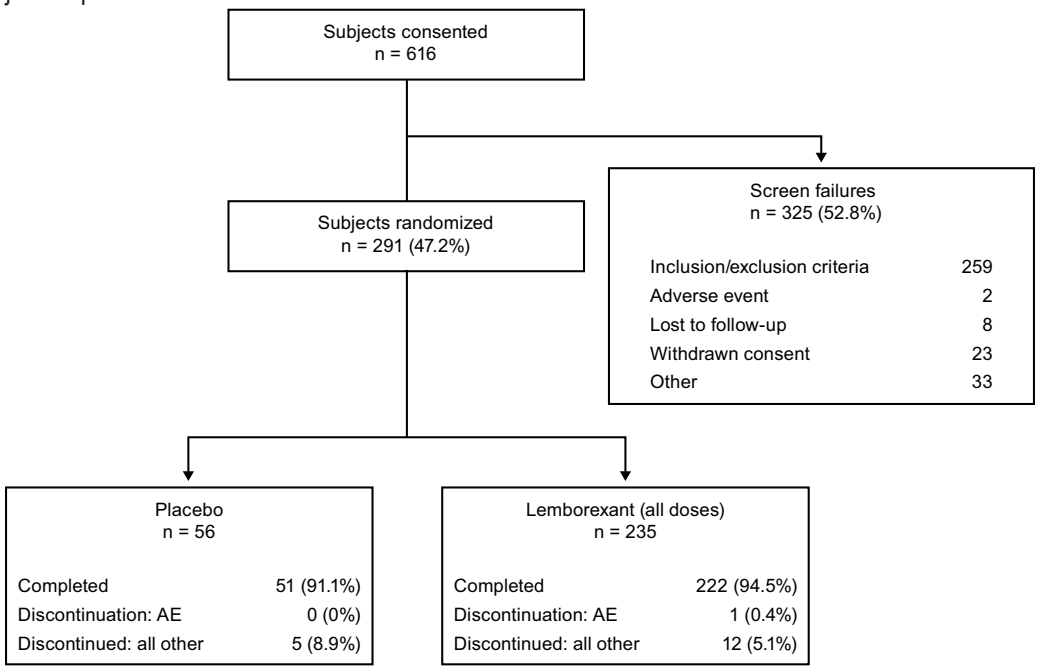
Safety and tolerability were assessed by adverse event (AE) reports and changes in vital signs, electrocardiograms (ECGs), clinical laboratory reports, and physical examinations. Potential for residual morning sleepiness was assessed using subjective (sleep diary and KSS) and objective measures (Digit Symbol Substitution Test [DSST] and a Reaction Time Task [RTT; simple reaction time and 5-choice reaction time]). On each morning in the clinic following a PSG recording, within 15 minutes, and at 1 hour and 2 hours after morning waketime, the KSS, a DSST, and a RTT were administered (**Figure 1**). AEs related to the mechanism of action of lemborexant that are associated with the sleep disorder narcolepsy (eg, sleep paralysis) were reported as designated compound-specific AEs of special interest and were documented in depth. Suicidality was assessed using the Columbia-Suicide Severity Rating Scale[22] at several time points throughout the study.

Analyses of relationships of pharmacokinetic parameters with pharmacodynamic markers and safety variables will be reported separately.

Statistical Analyses

Efficacy analyses were based on the full analysis set, defined as subjects who received ≥ 1 dose of study drug and had ≥ 1 postdose primary efficacy measurement. At each IA and at final analysis, the SE and KSS data were analyzed according to independent dose-response models. The active treatment arms for each endpoint were modeled with a normal dynamic linear model. Endpoints were then jointly assessed using utility functions. The adaptive aspects of the trial were based on the utility function. The utility was a function of the 2 endpoints, constructed by specifying the 1-dimensional component for each endpoint and then combining them multiplicatively.

Figure 2—Subject disposition.



AE = adverse event.

Adaptations as well as decisions regarding success and futility were based on the maximum utility dose, defined as the dose with highest mean utility. At each IA, the probability that the utility exceeded 1 at the maximum utility dose was computed and compared with prespecified early stopping criteria. The utility function had been constructed so that a utility above 1 corresponded to regions where efficacy and safety were both acceptable. The endpoint of KSS at days 15 and 16 was analyzed using a 90% confidence interval (CI) as described in the definition of acceptable KSS.

In addition to the Bayesian analysis, SE change from baseline to the mean of days 1 and 2 was analyzed using analysis of covariance, with treatment and baseline as fixed effects on the full analysis set. Analysis of KSS change from baseline to the mean of days 2 and 3 and to the mean of days 15 and 16 also used analysis of covariance, with treatment and baseline as fixed effects on the pharmacodynamics (PD) analysis set, defined as subjects who had sufficient PD data to derive at least 1 PD parameter. SE or KSS distributions were normalized by log-transformation before analysis and nonparametric methods were used for non-normally distributed data. Least squares mean (LSM) change from baseline, standard errors, differences between LSMs of placebo and each lemborexant dose (LSM difference from placebo), 95% CIs, and *P* values comparing LSM changes from baseline for placebo and each lemborexant dose were summarized.

Secondary efficacy and safety endpoints—SE, LPS, and WASO from the beginning of treatment and at end of treatment, and rebound insomnia—were analyzed using the same method as the SE component of the primary endpoint. Sleep diary parameters (sSE, sSOL, and sWASO) were similarly analyzed.

Incidence of AEs and change from baseline in laboratory values, ECG findings, vital signs, weight, and suicidality were summarized by treatment group using descriptive statistics on the safety analysis set, defined as subjects who received ≥ 1 dose of study drug and had ≥ 1 postdose safety assessment. Endpoints for residual morning sleepiness (KSS, DSST, and RTT) were analyzed using the same method as the KSS component of the primary endpoint.

Simulations showed that a maximum sample size of 300 subjects was sufficient to achieve a desirable chance of success for a wide range of different efficacy and residual morning sleepiness scenarios with an overall type I error rate of 2%. All statistical tests were based on the 5% level of significance, except for the Bayesian methods used for the primary endpoint.

RESULTS

Subject Disposition, Baseline Demographics, and Characteristics

A total of 616 subjects were screened, and 291 were randomized into the study (**Figure 2**). A total of 325 failed screening. Screen failures were mostly due to subjects not meeting inclusion/exclusion criteria (79.7%). The main reasons for screen failures included: not meeting PSG evidence of insomnia (27%), use of prohibited concomitant medications during the screening/baseline period prior to randomization (4.6%), or testing positive for use of illegal (or legalized) recreational drugs (3.9%). Baseline characteristics were similar between lemborexant groups and placebo (**Table 1**). Slightly more than 60% of subjects were female; the majority were white. Median age was 49.0 years (range: 19–80 years) in the lemborexant group and 46.5 years (range: 20–79 years) in the placebo group; 14.4% of all subjects were age 65 years or older. The most common subtype of insomnia, determined based on PSG findings,

Table 1—Baseline demographics and characteristics.

Category	Placebo (n = 56)	Lemborexant 1 mg (n = 32)	Lemborexant 2.5 mg (n = 27)	Lemborexant 5 mg (n = 38)	Lemborexant 10 mg (n = 32)	Lemborexant 15 mg (n = 56)	Lemborexant 25 mg (n = 50)	Lemborexant Total (n = 235)	Combined Total (n = 291)
Demographics									
Age, y*	47.1 (15.6)	53.3 (13.0)	49.7 (14.3)	51.1 (14.3)	47.1 (13.7)	44.0 (14.6)	48.9 (13.4)	48.5 (14.2)	48.3 (14.4)
Age, ≥ 65 y, %	16.1	21.9	14.8	21.1	15.6	7.1	10.0	14.0	14.4
Female, %	64.3	71.9	63.0	60.5	62.5	57.1	62.0	62.1	62.5
White, %	69.6	78.1	77.8	84.2	65.6	69.6	78.0	75.3	74.2
Black/ African American, %	26.8	21.9	18.5	7.9	21.9	26.8	16.0	19.1	20.6
American Indian/ Alaskan Native, %	0.0	0.0	0.0	2.6	3.1	0.0	2.0	1.3	1.0
Other race, %	3.6	0.0	3.7	5.3	9.4	3.6	4.0	4.3	4.1
BMI, kg/m^2*	26.8 (5.1)	26.9 (4.2)	26.3 (4.2)	26.6 (4.1)	26.3 (4.4)	27.0 (5.1)	26.6 (4.9)	26.7 (4.6)	26.7 (4.7)
PSG sleep*									
SE, %	66.6 (9.2)	61.7 (12.3)	61.3 (14.7)	63.1 (12.5)	65.1 (11.7)†	65.1 (12.2)	66.6 (10.9)	64.2 (12.3)‡	64.7 (11.8)§
LPS, min	58.8 (30.6)	69.9 (39.1)	73.0 (50.9)	70.4 (42.7)	67.9 (52.4)†	72.5 (36.1)	64.3 (45.9)	69.5 (43.6)‡	67.4 (41.6)§
WASO, min	108.9 (37.5)	121.2 (49.6)	119.8 (51.2)	113.7 (48.0)	103.5 (34.4)†	103.3 (42.9)	103.9 (40.5)	109.3 (44.4)‡	109.2 (43.1)§
Subjective sleep*									
sSE, %	62.8 (13.0)	63.4 (10.8)	65.8 (8.5)	66.0 (11.6)	66.4 (11.8)†	65.5 (11.3)	63.9 (11.3)	65.1 (11.0)‡	64.6 (11.4)§
sSOL, min	61.0 (32.0)	57.0 (27.1)	51.2 (15.0)	61.9 (36.7)	48.2 (27.9)†	63.6 (46.8)	62.4 (27.5)	58.7 (33.8)‡	59.1 (33.4)§
sWASO, min	118.4 (56.4)	115.8 (43.1)	113.1 (49.9)	102.7 (50.9)	108.7 (37.9)†	100.9 (38.9)	110.4 (50.2)	107.7 (45.2)‡	109.8 (47.6)§

* = data are presented as mean (standard deviation). † = n = 31. ‡ = n = 234. § = n = 290. BMI = body mass index, LPS = latency to persistent sleep, PSG = polysomnography, SE = sleep efficiency, sSE = subjective sleep efficiency, sSOL = subjective sleep onset latency, sWASO = subjective wakefulness after sleep onset, WASO = wake after sleep onset.

was mixed insomnia (ie, subjects exhibiting both sleep onset and sleep maintenance insomnia) (59.8%), followed by sleep maintenance insomnia only (29.2%), sleep onset insomnia only (9.6%), and other (1.4%). Baseline sleep parameters, including SE, LPS, WASO, sSE, sSOL, and sWASO, were similar among lemborexant dose groups and placebo (**Table 1**). The majority of subjects (lemborexant: 94.5%; placebo: 91.1%) completed the planned 15-day treatment regimen.

Primary Analysis—Utility Index

The study was stopped for early success after the fifth IA, which included data from 262 of the planned 300 subjects. At that analysis, 4 of the 6 doses (5, 10, 15, and 25 mg) met the utility index and KSS criteria for success, with 15 mg identified as the maximum utility dose; that is, this dose had the highest probability (93.5%) of having a utility index > 1, without unacceptable KSS at days 15 and 16. By the time this analysis was completed, an additional 29 subjects had been randomized, for a total n value of 291. At study completion, analysis of data from all 291 subjects showed that all 6 lemborexant doses met criteria for success (> 80% probability of having a utility index > 1, with acceptable KSS at days 15 and 16), with 15 mg again identified as the maximum utility dose.

Efficacy on Secondary Endpoints

Sleep Efficiency

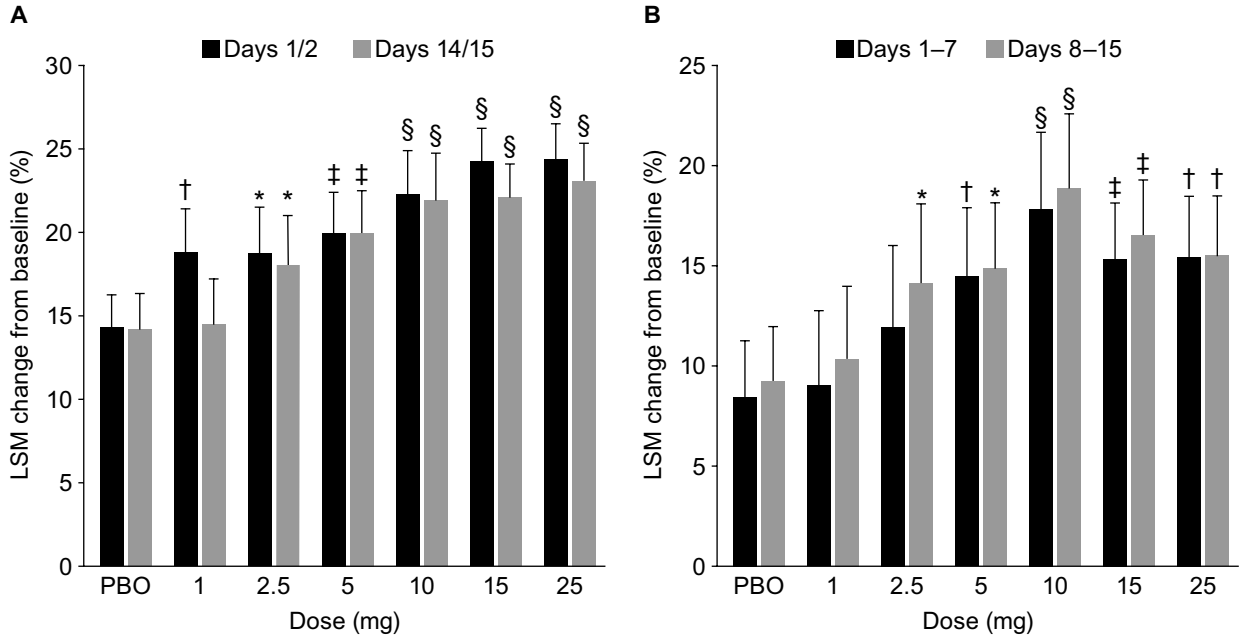
After the first 2 doses, all dose groups of lemborexant showed significantly greater improvement from baseline in LSM SE compared with placebo (**Figure 3A**; $P < .05$ for all doses; $P \leq .0001$ for doses ≥ 10 mg), with generally higher SE at higher lemborexant doses. The improvements in SE with lemborexant ranged from 4.4% (2.5 mg dose) to 10.1% (15 and 25 mg doses) above the placebo percentage. Findings were similar after the last 2 doses on days 14 and 15, with statistically significant improvement from baseline compared with placebo for all lemborexant dose groups ≥ 2.5 mg ($P < .05$ for doses ≥ 2.5 mg; $P < .0001$ for doses ≥ 10 mg). The improvements in SE with lemborexant ranged from 0.3% (1 mg) to 8.9% (25 mg) above the placebo percentage.

Similar to these PSG results, there was generally substantially greater improvement from baseline in LSM sSE on lemborexant compared with placebo (**Figure 3B**). Statistically significant improvements in mean sSE compared with placebo were observed at lemborexant doses of ≥ 5 mg on days 1 to 7 ($P < .01$), with differences ranging from 6.0% (5 mg) to 9.4% (10 mg) higher than placebo. On days 8 to 15, significant improvement in LSM sSE compared with placebo was observed at doses of ≥ 2.5 mg ($P < .05$ for doses ≥ 2.5 mg; $P < .01$ for doses ≥ 10 mg), with differences ranging from 4.9% (2.5 mg) to 9.5% (10 mg) higher than placebo.

Sleep Onset

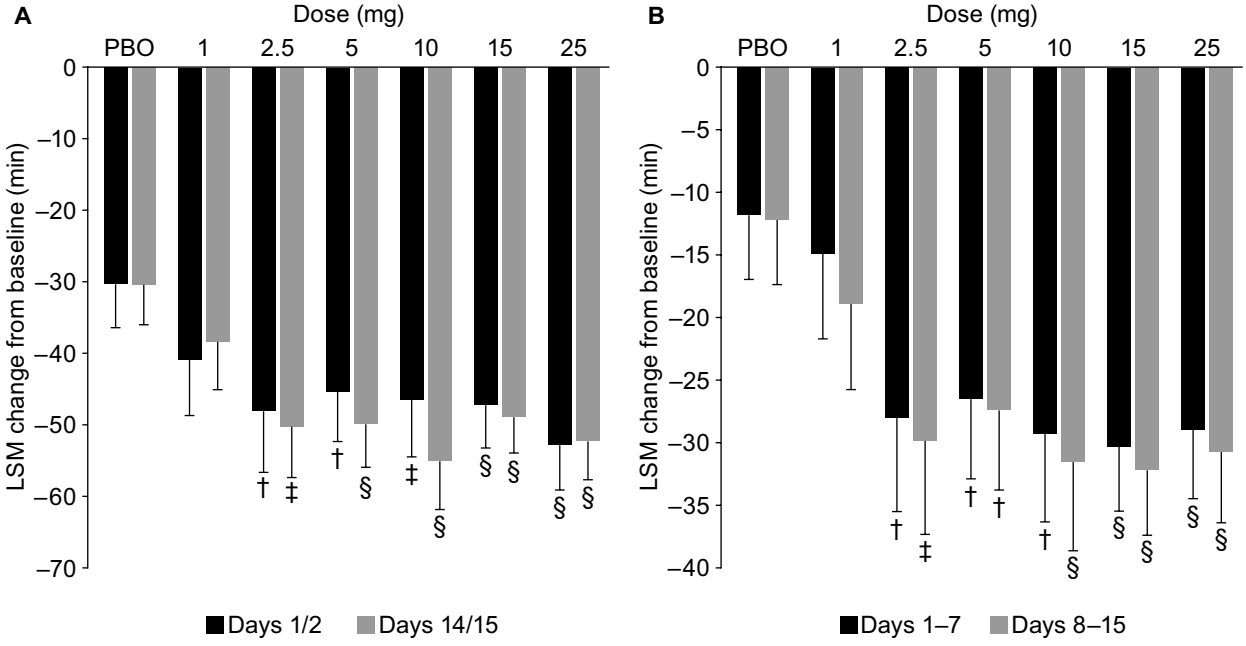
After the first 2 doses, all dose groups of lemborexant experienced greater decreases from baseline in LSM LPS compared with placebo (**Figure 4A**). Because LPS was not normally distributed, comparisons were conducted using the geometric mean ratio (active dose/placebo), which showed

Figure 3—Sleep efficiency.



Sleep efficiency as measured by **(A)** polysomnography and **(B)** sleep diary. * = $P < .05$. † = $P < .01$. ‡ = $P < .001$. § = $P \leq .0001$. *P* values calculated based on differences in least squares mean (LSM) changes from baseline between lemborexant and placebo (PBO). Error bars represent upper confidence interval.

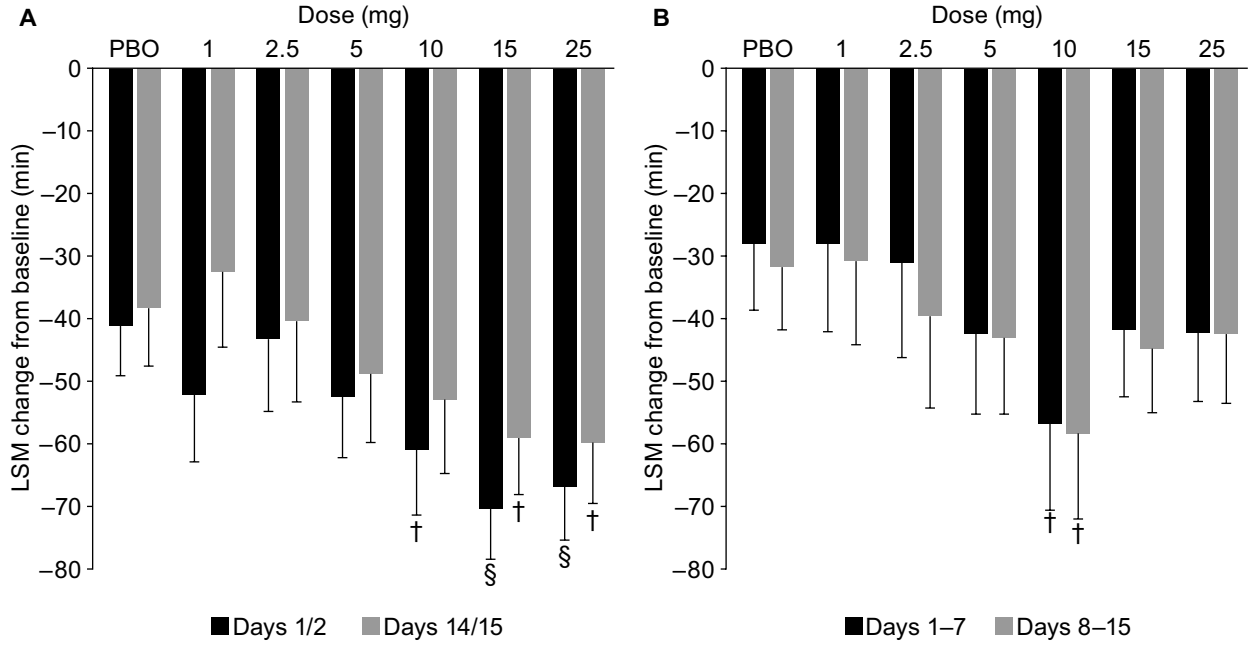
Figure 4—Latency to persistent sleep and sleep onset latency.



(A) Latency to persistent sleep as measured by polysomnography and **(B)** sleep onset latency as measured by sleep diary. † = $P < .01$. ‡ = $P \leq .001$. § = $P \leq .0001$. *P* values calculated based on differences in geometric mean ratio between lemborexant and placebo (PBO). Error bars represent lower confidence interval (CI). LPS/sSOL are not considered normally distributed, but for ease of presentation of data, adjusted LSMs and 95% CIs are shown here. LPS = latency to persistent sleep, LSM = least squares mean, sSOL = subjective sleep onset latency.

a statistically significant decrease in mean LPS compared with placebo in lemborexant dose groups ≥ 2.5 mg ($P < .01$ for doses ≥ 2.5 mg; $P < .001$ for doses ≥ 10 mg). A generally shorter LPS was seen as lemborexant dose increased. The decreases in median LPS with lemborexant ranged from 1.5 (1 mg) to 13.8 (25 mg) minutes greater than with placebo. Similarly, following the last 2 doses, decreases from baseline in LSM LPS were significantly greater than placebo at lemborexant doses of ≥ 2.5 mg ($P < .01$ for doses ≥ 2.5 mg; $P < .001$ for doses ≥ 10 mg). The decreases in median LPS

Figure 5—Wake after sleep onset.



Wake after sleep onset as measured by **(A)** polysomnography and **(B)** sleep diary. † = $P < .01$. § = $P \leq .0001$. *P* values calculated based on differences in least squares mean (LSM) changes between lemborexant and placebo (PBO). Error bars represent lower confidence interval.

with lemborexant ranged from 7.0 (1 mg) to 17.3 (25 mg) minutes greater than with placebo.

Sleep diary results were similar; all dose groups of lemborexant experienced greater decreases from baseline in LSM sSOL compared with placebo (**Figure 4B**). These changes were statistically significant at lemborexant doses ≥ 2.5 mg ($P < .01$) on days 1 to 7. The decreases in median sSOL with lemborexant ranged from 3.2 (1 mg) to 18.5 (10 mg) minutes greater than with placebo. On days 8 to 15, statistical improvements in LSM sSOL compared with placebo were observed for lemborexant doses ≥ 2.5 mg ($P < .01$). The decreases in median sSOL with lemborexant ranged from 7.1 (1 mg) to 20.9 (10 mg) minutes greater than with placebo.

Sleep Maintenance

After the first 2 doses, all dose groups of lemborexant showed greater decreases from baseline in LSM WASO compared with placebo (**Figure 5A**), and these decreases were significantly greater for lemborexant dose groups of ≥ 10 mg ($P < .01$). The decreases in WASO with lemborexant ranged from 2.3 (2.5 mg) to 29.3 (15 mg) minutes greater than with placebo. After the last 2 doses, decrease from baseline in LSM WASO was significantly greater compared with placebo for lemborexant doses of ≥ 15 mg ($P < .01$). The differences in WASO with lemborexant ranged from an increase of 5.7 minutes (1 mg) to a decrease of 21.5 minutes (25 mg) compared with placebo.

Sleep diary results showed a similar trend (**Figure 5B**). For days 1 to 7, subjects treated with lemborexant reported numerically greater decreases from baseline in LSM sWASO than did subjects treated with placebo for all dose groups of lemborexant, despite a relatively large improvement in LSM sWASO in the placebo group. This decrease from baseline in LSM sWASO was significantly greater than that for placebo at the 10-mg dose ($P < .01$), but the observed trends did not reach statistical significance at the other doses of lemborexant. Treatment with lemborexant resulted in decreases in sWASO with differences ranging from 0.1 (1 mg) to 28.6 (10 mg) minutes. Results were similar for days 8 to 15. Subjects treated with all doses of lemborexant except 1 mg reported numerically greater decreases from baseline in LSM sWASO, with the 10-mg dose reaching statistical significance ($P < .01$). The differences in sWASO with lemborexant ranged from an increase of 0.7 (1 mg) to a decrease of 26.6 (10 mg) minutes compared with placebo.

Durability of Effect

Lemborexant demonstrated a durability of effect from the beginning to the end of treatment. Based on placebo-corrected comparisons, the improvements from baseline in LSM SE after administration of lemborexant on days 14 and 15 did not differ significantly from those after lemborexant on days 1 and 2. Similarly, changes in LSM WASO did not differ over this treatment interval. In fact, mean LPS was numerically shorter on days 14 and 15 for all doses except for 1 mg and 25 mg, as compared with days 1 and 2; at the 10-mg dose, this comparison reached statistical significance ($P < .05$), suggesting an increase in efficacy from beginning to end of treatment.

The increases from baseline in LSM sSE values for days 8 to 15 were not significantly different from those for days 1 to 7 for any dose of lemborexant. For sSOL, this was observed for doses of 2.5 mg to 25 mg. Consistent with sSE and similar to sSOL, sWASO results for days 8 to 15 were not significantly different from those for days 1 to 7 for all doses. These sleep diary results are consistent with PSG results, further supporting that

Table 2—Summary of adverse events by placebo and lemborexant treatment.

		Lemborexant					
	Placebo (n = 56)	1 mg (n = 32)	2.5 mg (n = 27)	5 mg (n = 38)	10 mg (n = 32)	15 mg (n = 56)	25 mg (n = 50)
TEAEs	37.5	34.4	40.7	42.1	59.4	55.4	60.0
Treatment-related TEAEs	19.6	25.0	33.3	31.6	46.9	42.9	48.0
Serious TEAEs	1.8	0.0	0.0	0.0	0.0	0.0	2.0
TEAEs leading to discontinuation	0.0	0.0	0.0	0.0	0.0	0.0	2.0
Common AEs*							
Somnolence	0.0	3.1	3.7	5.3	12.5	17.9	22.0
Headache	5.4	9.4	11.1	7.9	9.4	10.7	10.0
Sleep paralysis	0.0	0.0	0.0	2.6	9.4	7.1	4.0
Rapid eye movements abnormal sleep	3.6	0.0	7.4	2.6	3.1	5.4	4.0
Nightmare	0.0	0.0	0.0	2.6	9.4	7.1	0.0
Abnormal dreams	0.0	6.3	0.0	2.6	9.4	0.0	0.0
Dizziness	5.4	0.0	3.7	5.3	0.0	3.6	2.0
Back pain	0.0	0.0	3.7	0.0	3.1	5.4	0.0
Hypnagogic hallucinations	0.0	0.0	0.0	2.6	3.1	3.6	2.0
Myalgia	0.0	0.0	0.0	7.9	3.1	1.8	0.0
Feeling drunk	0.0	0.0	0.0	0.0	0.0	0.0	6.0

Data are presented as % of subjects reporting given adverse event. * = ≥ 5% in any lemborexant group. AEs = adverse events, TEAEs = treatment-emergent adverse events.

the effect of lemborexant was maintained across the 15-night treatment duration.

Potential for Rebound Insomnia

On days 16 and 17, change from baseline in LSM SE, LPS, or WASO was not significantly different from placebo for any dose of lemborexant, indicating that on those nights, sleep was not worse than at baseline as a result of having taken and then abruptly discontinued treatment with lemborexant. Sleep diary data from the 2 weeks posttreatment are consistent with the PSG data for the 2 days after discontinuation of lemborexant treatment in that the data provided no evidence for rebound insomnia.

Safety and Tolerability

Adverse Events and Other Safety Measures

Lemborexant was generally well tolerated; only 1 subject (in the 25-mg group) discontinued because of a treatment-emergent adverse event (TEAE).

The overall incidence of TEAEs with lemborexant (50.2%) was higher than with placebo (37.5%; **Table 2**). The most common TEAE (≥ 5%) was somnolence, which appeared dose-related with a frequency of 3.1% in the 1 mg group rising to 22.0% in the 25-mg group. Reports of somnolence were generally associated with the first or second dose. Ten subjects (4.3%) who received lemborexant at doses ≥ 5 mg experienced sleep paralysis, but none discontinued the study as a result. The sleep paralysis events were transient and typically occurred around the time of sleep onset (within 1 hour postdose) after the first 1 or 2 doses while the patients were in bed, and did not persist for the duration of the study. Two episodes of potential cataplexy that lasted 3 to 4 minutes were reported approximately 14 hours postdose on consecutive days in a subject taking 15 mg lemborexant; this was considered by the investigator to be mild and probably related to the investigational drug. The potential cataplexy events resolved without sequelae.

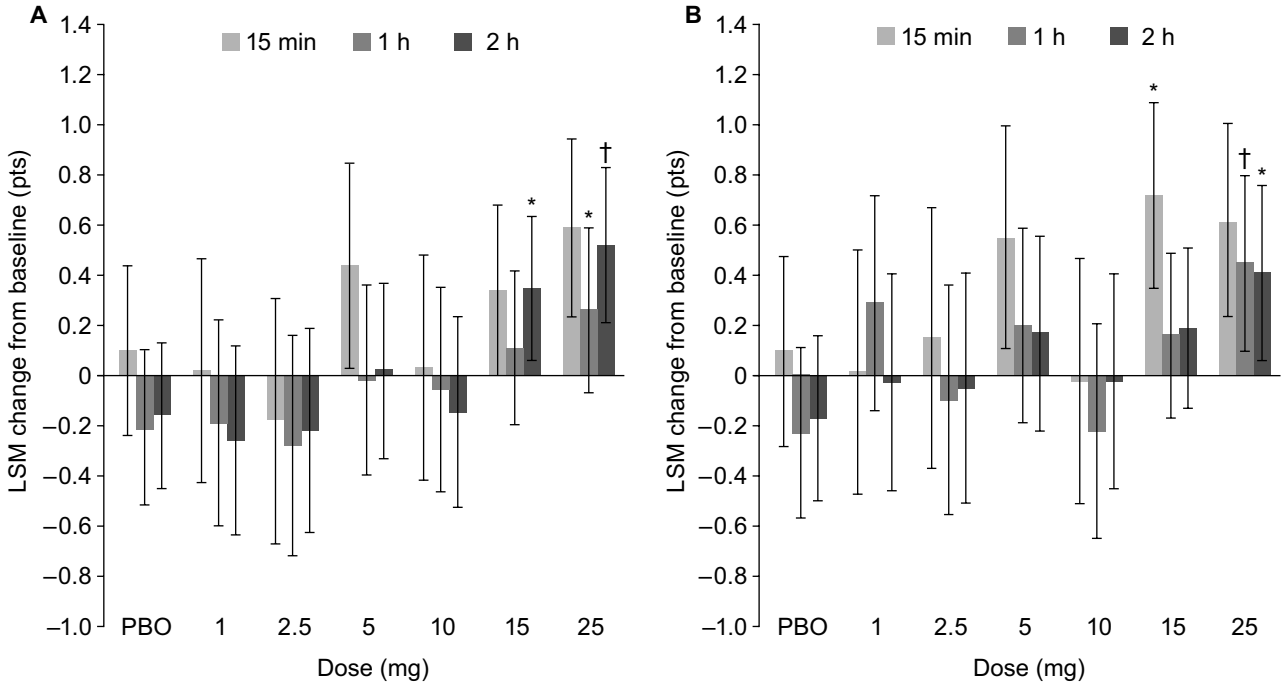
Two serious TEAEs occurred in the study (**Table 2**). One subject in the placebo group with no known history of hyperkalemia experienced hyperkalemia (considered not related to study drug), and 1 subject in the 25-mg group with no known seizure history had 2 focal-onset seizures (considered possibly related to study drug) after receiving the second dose of the study drug. The latter subject discontinued the study after 2 days of dosing with no sequelae and was the only subject to discontinue treatment because of an AE. Magnetic resonance imaging in this patient revealed 2 small lobulations involving the paraclinoid segment left internal carotid flow-void that potentially may represent small aneurysms. The location of these lesions in the left hemisphere could suggest that either might be the seizure focus.

There were no clinically important differences between lemborexant treatment and placebo on blood chemistry, vital signs, weight, or ECG. In addition, no suicidal behavior or suicidal ideation was reported during the study.

Potential for Residual Morning Sleepiness

On days 2 and 3, within 15 minutes and at 1 hour and 2 hours after waketime, the mean change from baseline on KSS did not differ significantly from placebo at doses from 1 mg to 10 mg (**Figure 6**). KSS was significantly increased from baseline with lemborexant versus placebo (respectively, LSM difference

Figure 6—KSS scores.



KSS scores at the **(A)** beginning and **(B)** end of treatment, graphed as a function of time relative to morning waketime (KSS is a 9-point Likert-type scale on which subjects rate their current level of sleepiness). * = $P < .05$. † = $P < .01$. *P* values calculated based on differences in least squares mean (LSM) changes between lemborexant and placebo. Error bars represent confidence intervals. KSS = Karolinska Sleepiness Scale, pts = points.

between lemborexant and placebo [95% CI]), with 15 mg at 2 hours (0.51 [0.10, 0.92]; $P = .0140$) and with 25 mg at 1 hour (0.47 [0.02, 0.93]; $P = .0393$) and 2 hours (0.68 [0.26, 1.10]; $P = .0016$) after waketime. Similarly, on days 15 and 16, there were statistically significant increases in KSS from baseline versus placebo (respectively, LSM [95% CI]), with 15 mg at 15 minutes (0.62 [0.09, 1.15]; $P = .0226$) and 25 mg at 1 hour (0.68 [0.19, 1.17]; $P = .0063$) and 2 hours (0.59 [0.10, 1.07]; $P = .0173$) after waketime. Statistical comparisons between days 2 and 3 versus days 15 and 16 did not show any significant differences between beginning and end of treatment, confirming that there were minimal or no changes in KSS after waketime during the 15-night treatment duration.

For the simple reaction test, 5-choice reaction time, and DSST, there were no consistent overall effects of lemborexant as compared with placebo on either days 2 and 3 or days 15 and 16. There were no significant or dose-related changes from baseline at any dose and at any time point on either days 2 and 3 or days 15 and 16 for the 5-choice reaction time.

DISCUSSION

In this proof-of-concept trial, lemborexant doses ranging from 1 mg to 25 mg all met both primary endpoints by exceeding the prespecified thresholds for the balance between efficacy and safety at study completion.

Lemborexant had a positive effect on SE by improving both sleep onset (decreasing LPS) and sleep maintenance (decreasing WASO) in a dose-related manner. The increases in SE, ranging from approximately 5% at 1 mg to 10% at 25 mg, indicate that during the 8-hour sleep opportunity evaluated, subjects slept an average of approximately 24 to 48 minutes longer than those who received placebo. These changes were larger than for placebo at all doses of lemborexant, even with the expected large placebo response,[23–25] and were maintained at the end of 15 nights of treatment for lemborexant dose groups ≥ 2.5 mg.

In this study, subjects treated with lemborexant exhibited improved sleep on both objective and subjective measures, with overall close concordance between PSG measures and sleep diary results. This alignment between objective and subjective sleep measure results is noteworthy; patient self-reports are often not in agreement with objective measures even in the absence of treatment.[26–28] Given that insomnia has subjective components, effective treatments should impact a subject's perceived improvement in the amount of sleep obtained.

Overall, lemborexant was well tolerated. Rates of somnolence showed evidence of dose response in the lemborexant groups compared with placebo. However, no subject discontinued either treatment or the study because of somnolence. Sleep paralysis occurred in a small number of subjects. This adverse event is consistent with the known pharmacology of orexin receptor antagonism and has been reported in subjects receiving other DORAs.[29–32] Two transient episodes that may be considered cataplexy were reported in 1 subject with the 15-mg dose.

Lemborexant was not associated with clinically meaningful residual morning sleepiness over time. No significant increases

in residual morning sleepiness (within 15 minutes, at 1 hour, and at 2 hours) were experienced by subjects treated with lemborexant doses of 1 mg to 10 mg as measured by the KSS. Doses of 15 mg and 25 mg lemborexant at some time points were associated with small (< 1 point), statistically significant but not clinically meaningful increases in sleepiness on the KSS compared with placebo. There was also no evidence of rebound insomnia after cessation of treatment with any dose of lemborexant as measured by PSG or sleep diary.

Interest in the orexin system as a target for developing insomnia treatments has been driven by loss of efficacy over time with some non-DORA pharmacologic treatments,[9,14] as well as safety concerns such as daytime sleepiness (potentially leading to next-day driving impairments), rebound insomnia, cognitive impairment, complex sleep-related behaviors, and increased risk of falls,[9,10,33,34] particularly in the middle of the night. In this study, treatment with lemborexant did not result in excessive daytime sleepiness or rebound insomnia, and no aberrant nocturnal behaviors were reported. Current theoretical understanding of the mechanism of action of DORAs suggests they would be less likely to cause complex sleep-related behaviors that have been associated with the use of some hypnotic drugs,[29,35] and findings from the current study provide further support for this hypothesis. Future studies will examine these issues with insomnia treatments in greater detail and will further elucidate the efficacy and safety profile of lemborexant.

The study included approximately 15% of subjects age 65 years or older. Although the elderly represent a significant population suffering from insomnia,[36,37] these subjects often have comorbid conditions requiring medications that complicate their insomnia treatment,[37] making them a particularly important yet challenging group to study directly. Another strength of this study, the use of Bayesian adaptive design and RAR, allowed for efficient evaluation of a wide range of doses (from below the minimum anticipated therapeutic dose to beyond the maximum anticipated therapeutic dose) and facilitated selection of the best doses for study in the phase 3 trials.

The primary limitation of this study was its 15-day treatment duration, which did not allow the assessment of long-term efficacy or the development of tolerance to the benefits or side effects of the drug; the long-term use of common medications for insomnia has been associated with safety concerns such as the potential for addiction and rebound insomnia.[11,38]

CONCLUSIONS

Lemborexant doses ranging from 2.5 mg to 25 mg improved SE and decreased sleep latency; doses ≥ 5 mg also decreased the amount of time spent awake after sleep onset, with doses ≥ 10 mg having a statistically significant effect. Improvements were found on both objective and subjective measures. The effects were apparent during the first 2 nights of treatment and generally persisted for the 15 nights of treatment. Doses above 10 mg did not show consistently greater efficacy than the 10 mg dose and were associated with higher rates of somnolence. At doses up to 10 mg, lemborexant was not associated with residual next-morning sleepiness on either subjective or objective assessments. Lemborexant was generally well tolerated and had an acceptable safety profile. Results from this study suggest that doses from 2.5 mg to 10 mg are the most appropriate doses to take forward for further evaluation.

ABBREVIATIONS

AE, adverse event
CI, confidence interval
DORA, dual orexin receptor antagonist
DSST, Digit Symbol Substitution Test
ECG, electrocardiogram
IA, interim analysis
KSS, Karolinska Sleepiness Scale
LPS, latency to persistent sleep
LSM, least squares mean
PD, pharmacodynamics
PSG, polysomnography
RAR, response adaptive randomization
RTT, Reaction Time Task
SE, sleep efficiency
sSE, subjective sleep efficiency
sSOL, subjective sleep onset latency
sWASO, subjective wakefulness after sleep onset
TEAE, treatment-emergent adverse event
WASO, wake after sleep onset

REFERENCES

1. Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med.* 2007;3(5 Suppl):S7–S10.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health*. 4th ed. Washington DC: American Psychiatric Association; 1994.
3. Ohayon MM, Reynolds CF 3rd. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). *Sleep Med.* 2009;10(9):952–960.
4. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord.* 2011;135(1–3):10–19.
5. Kessler RC, Berglund PA, Coulouvrat C, et al. Insomnia and the performance of US workers: results from the America Insomnia Survey. *Sleep.* 2011;34(9):1161–1171.
6. Neubauer DN. The evolution and development of insomnia pharmacotherapies. *J Clin Sleep Med.* 2007;3(5 Suppl):S11–S15.
7. Rosenberg RP. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Ann Clin Psychiatry.* 2006;18(1):49–56.
8. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med.* 2008;4(5):487–504.
9. Equihua AC, De La Herrán-Arita AK, Drucker-Colin R. Orexin receptor antagonists as therapeutic agents for insomnia. *Front Pharmacol.* 2013;4:163.
10. Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ.* 2005;331(7526):1169.
11. Wilt TJ, MacDonald R, Brasure M, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med.* 2016;165(2):103–112.
12. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2016;165(2):125–133.

13. Zammit G, Wang-Weigand S, Rosenthal M, Peng X. Effect of ramelteon on middle-of-the-night balance in older adults with chronic insomnia. *J Clin Sleep Med*. 2009;5(1):34–40.
14. Soldatos CR, Dikeos DG, Whitehead A. Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. *Int Clin Psychopharmacol*. 1999;14(5):287–303.
15. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2011;51:243–266.
16. Kumar A, Chanana P, Choudhary S. Emerging role of orexin antagonists in insomnia therapeutics: an update on SORAs and DORAs. *Pharmacol Rep*. 2016;68(2):231–242.
17. Sutton EL. Profile of suvorexant in the management of insomnia. *Drug Des Devel Ther*. 2015;9:6035–6042.
18. Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep*. 2013;36(2):259–267.
19. Walsh JK, Salkeld L, Knowles LJ, Tasker T, Hunneyball IM. Treatment of elderly primary insomnia patients with EVT 201 improves sleep initiation, sleep maintenance, and daytime sleepiness. *Sleep Med*. 2010;11(1):23–30.
20. Ivanova A, Liu K, Snyder E, Snavely D. Insomnia and the performance of US workers: results from the America insomnia survey. *Sleep*. 2011;34(9):1161–1171.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington DC: American Psychiatric Association; 2013.
22. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277.
23. Bélanger L, Vallières A, Ivers H, Moreau V, Lavigne G, Morin CM. Meta-analysis of sleep changes in control groups of insomnia treatment trials. *J Sleep Res*. 2007;16(1):77–84.
24. McCall WV, D'Agostino R Jr, Dunn A. A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. *Sleep Med*. 2003;4(1):57–62.
25. Winkler A, Rief W. Effect of placebo conditions on polysomnographic parameters in primary insomnia: a meta-analysis. *Sleep*. 2015;38(6):925–931.
26. Bianchi MT, Williams KL, McKinney S, Ellenbogen JM. The subjective-objective mismatch in sleep perception among those with insomnia and sleep apnea. *J Sleep Res*. 2013;22(5):557–568.
27. Carskadon MA, Dement WC, Mitler MM, Guilleminault C, Zarcone VP, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. *Am J Psychiatry*. 1976;133(12):1382–1388.
28. Silva GE, Goodwin JL, Sherrill DL, et al. Relationship between reported and measured sleep times: the sleep heart health study (SHHS). *J Clin Sleep Med*. 2007;3(6):622–630.
29. Brisbare-Roch C, Dingemanse J, Koberstein R, et al. Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med*. 2007;13(2):150–155.
30. De la Herrán-Arita AK, Guerra-Crespo M, Drucker-Colin R. Narcolepsy and orexins: an example of progress in sleep research. *Front Neurol*. 2011;2:26.
31. Herring WJ, Connor KM, Ivgy-May N, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biol Psychiatry*. 2016;79(2):136–148.
32. Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2014;13(5):461–471.
33. Panneman MJ, Goettsch WG, Kramarz P, Herings RM. The costs of benzodiazepine-associated hospital-treated fall Injuries in the EU: a Pharmo study. *Drugs Aging*. 2003;20(11):833–839.
34. Verster JC, Veldhuijzen DS, Patat A, Olivier B, Volkerts ER. Hypnotics and driving safety: meta-analyses of randomized controlled trials applying the on-the-road driving test. *Curr Drug Saf*. 2006;1(1):63–71.
35. Peever J, Luppi PH, Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci*. 2014;37(5):279–288.
36. Jaussent I, Dauvilliers Y, Ancelin ML, et al. Insomnia symptoms in older adults: associated factors and gender differences. *Am J Geriatr Psychiatry*. 2011;19(1):88–97.
37. Sivertsen B, Nordhus IH. Management of insomnia in older adults. *Br J Psychiatry*. 2007;190:285–286.
38. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007;22(9):1335–1350.

ACKNOWLEDGMENTS

The authors acknowledge Deborah Stull, PhD, and Nicholas C. Stilwell, PhD, of Evidence Scientific Solutions for providing writing and editorial support. This support was funded by Eisai Inc. The authors also thank the following investigators: Jonathan Flescher, MD, Wake Research Associates - Carolina Phase I, Raleigh, NC; Steven Hull, Vince and Associates Clinical Research, Overland Park, KS; David Seiden, Broward Research Group, Hollywood, FL; Vishaal Mehra, Artemis Institute for Clinical Research, San Diego, CA; Mark Gotfried, Pulmonary Associates, PA, Phoenix, AZ; Howard Schwartz, Miami Research Associates, South Miami, FL; Andrew Klymiuk, KRK Medical Research, Dallas, TX; James Perlstrom, Sleep Disorders Center of the Mid-Atlantic, Vienna, VA; Maha Ahmad, Clinilabs, Inc., New York, NY; John Hudson, FutureSearch Trials of Neurology & Sleep Lab, LP, Austin, TX; Beth Safirstein, MD Clinical, Hallandale Beach, FL; Milton Erman, Pacific Sleep Medicine Medical Corp, Oceanside, CA; Stephen Thein, Pacific Research Network, Inc., San Diego, CA; Steven Folkerth, Clinical Research Center of Nevada LLC, Las Vegas, NV; Daniel Lorch, PAB Clinical Research & Florida Sleep Disorder Clinic, Brandon, FL; Jane Dyonzak, Chicago Research Center, Chicago, IL; Brock Summers, Southern California Research, LLC, Thousand Oaks, CA; John Murphy, Southern California Research, LLC, Fountain Valley, CA; Kurt Lesh, Lynn Institute of the Rockies, Colorado Springs, CO; June Fry, Center for Sleep Medicine Chestnut Hill Hospital, Philadelphia, PA; Richard Bogan, SleepMed of South Carolina, Columbia, SC.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February 6, 2017
Submitted in final revised form August 7, 2017
Accepted for publication August 25, 2017
Address correspondence to: Patricia Murphy, PhD, Eisai Inc, 100 Tice Boulevard, Woodcliff Lake, NJ 07677; Tel: (201) 949-4856; Fax: (201) 949-4595; Email: Patricia_Murphy@eisai.com

DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at Eisai Inc. This study included the investigational use of lemborexant. This study was funded by Eisai Inc. Patricia Murphy, Margaret Moline, Kate Pinner, Shobha Dhadda, Quan Hong, Luigi Giorgi, and Andrew Satlin are employees (or former employees) of Eisai Inc. David Mayleben has received grant/research support and has served as a consultant for Eisai Inc. Russell Rosenberg has received grant/research support from Actelion Pharmaceuticals, Eisai Inc., Flamel Pharmaceuticals, Jazz Pharmaceuticals, Merck, and Philips Respironics, has investigational device/drug interest with Eisai, Inc., Flamel Pharmaceuticals and Jazz Pharmaceuticals, and has served on the speakers bureau for Merck. Gary Zammit has received grant/research support from AbbVie, Actelion Pharmaceuticals, Adare Pharmaceuticals, Alder Biopharmaceuticals, Alkermes, AstraZeneca, Balance Therapeutics, BioMarin Pharmaceutical, CHDI Foundation, Eisai, Inc., Flamel Technologies, Flex Pharma, Janssen Pharmaceutical, Jazz Pharmaceuticals, Merck, Neurocrine Biosciences, Pfizer, Purdue Pharma, Sequential Medicine, and Takeda Pharmaceutical Company, has served as a consultant for Eisai Inc., Janssen Pharmaceutical, and Purdue Pharma, and has served on the speakers bureau for Merck.