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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

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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

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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%.

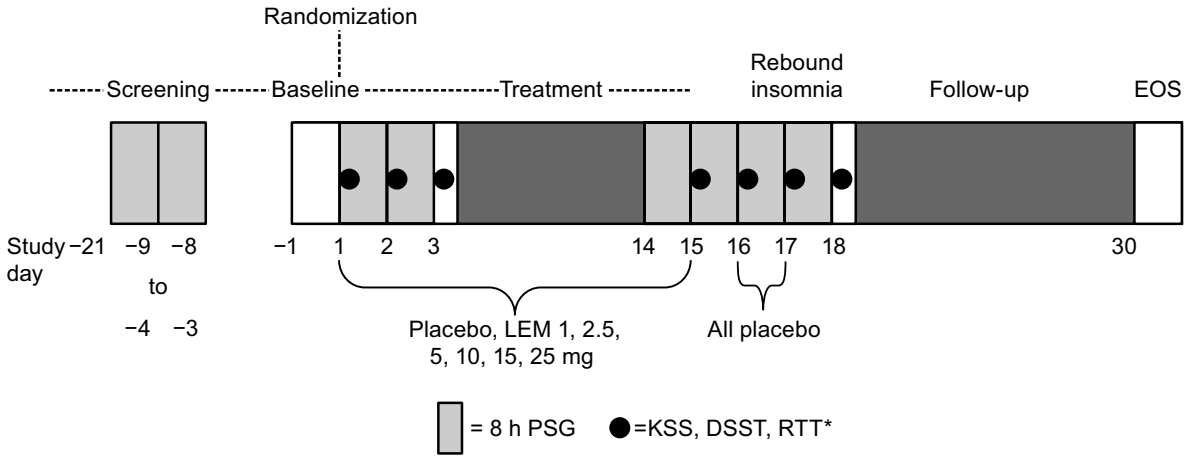
Secondary objectives were evaluated by additional PSG measures of sleep improvement comparing each dose of lemborexant with placebo. Efficacy at the beginning of treatment was measured as change from mean at baseline to mean after dosing on day 1 and day 2 for SE (overall efficacy), latency to persistent 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

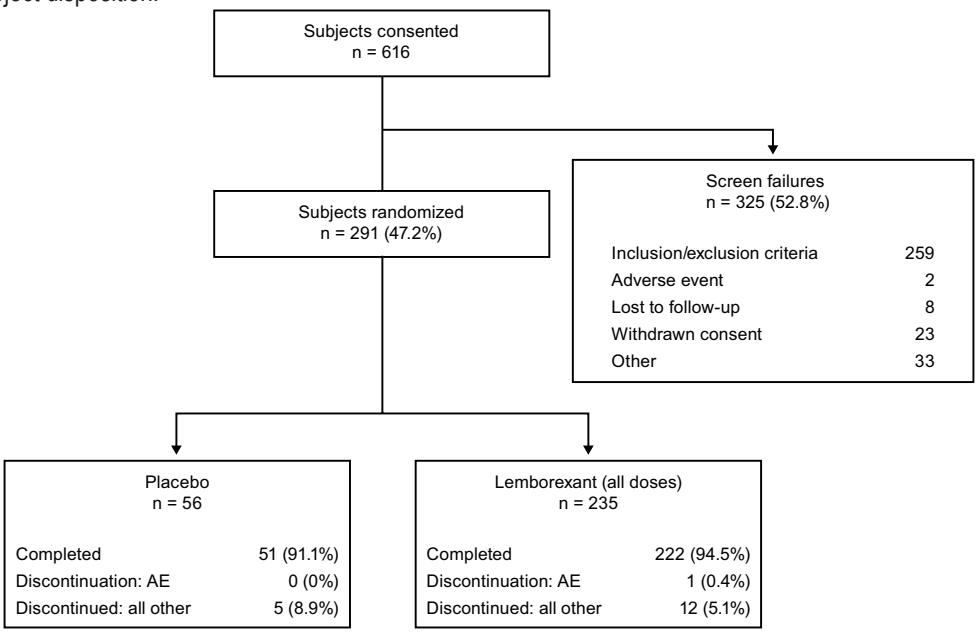
Safety and tolerability were assessed by adverse event (AE) reports and changes in vital signs, electrocardiograms (ECGs), clinical laboratory reports, and physical examinations. Potential for residual morning sleepiness was assessed using subjective (sleep diary and KSS) and objective measures (Digit 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

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