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Abuse Potential of Lemborexant, a Dual Orexin Receptor Antagonist, Compared With Zolpidem and Suvorexant in Recreational Sedative Users

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Abstract:

Background: Lemborexant (LEM) is a dual orexin receptor antagonist approved for the treatment of insomnia in adults in multiple countries including the United States, Japan, Canada, Australia and several Asian countries.

Procedures: This was a randomized, single-dose, single-center, double-blind, active-control, 6-way crossover study to evaluate LEM abuse potential. The study assessed oral doses of LEM 10 mg (LEM10), 20 mg (LEM20), and 30 mg (LEM30) compared with placebo (PBO), zolpidem (ZOL) immediate release 30 mg, and suvorexant (SUV) 40 mg. Subjects were healthy, nondependent, recreational sedative users able to discriminate/like the effects of both SUV and ZOL from PBO during a qualification phase.

Results: Abuse potential endpoints were analyzed in qualified subjects who received and completed all treatments ($n = 32$). On the “at this moment” drug-liking visual analog scale (VAS), mean maximum (peak) effect (primary endpoint) values were 78.4, 80.5, and 83.6 for LEM10, LEM20, and LEM30, respectively, which were all significantly greater than PBO (57.8; all $P > 0.05$) but not different from SUV (76.1) or ZOL (78.3). Similarly, for secondary endpoints overall drug-liking VAS and take-drug-again VAS, mean maximum (peak) effect values for all LEM doses were significantly greater than PBO ($P > 0.05$) but not different compared with ZOL or SUV.

Conclusions: For all doses, LEM demonstrated abuse potential versus PBO and appeared to have a similar abuse potential profile to ZOL and SUV in this study population. Lemborexant was well tolerated. Lemborexant has been placed in Schedule IV, the same drug schedule as ZOL and SUV.

Key Words: abuse potential study, insomnia, lemborexant, orexin agonist

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Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved in multiple countries, including the United States, Japan, Canada, Australia and several Asian countries, for the treatment of insomnia in adults. The sleep-promoting mechanism of action of DORAs is different from benzodiazepines

and “z drugs.” Antagonism of orexin receptors by DORAs suppresses inappropriate wakefulness, in contrast to benzodiazepine hypnotics and z drugs that instead promote sleep through a GABAergic mechanism of action.^{1,2} As required for US marketing approval for new compounds with central nervous system-sedating effects, the abuse potential of LEM was assessed in a phase 1 human abuse potential study in accordance with US Food and Drug Administration (FDA) guidance.³

In the pivotal phase 3 studies in subjects with insomnia disorder, Study E2006-G000-304 (Study 304; SUNRISE-1; NCT02783729) and Study E2006-G00-303 (Study 303; SUNRISE-2; NCT02952820), LEM provided significant benefits for sleep onset and sleep maintenance compared with placebo (PBO).^{4,5} At therapeutic doses of LEM 5 mg (LEM5) or 10 mg (LEM10), LEM was well tolerated with low rates of discontinuation. Adverse event (AE) rates were low and mostly mild, with somnolence the most commonly reported AE.^{4,5} The rate of AEs associated with abuse potential was low (ie, there was no euphoria reported) for subjects receiving LEM in the phase 3 studies.

Although a higher incidence of potential abuse-related treatment-emergent AEs (TEAEs) was observed with LEM compared with PBO in the phase 3 studies,^{4,6} this effect was driven by somnolence (rates of somnolence were 1.6%, 8.6%, and 13.1% for PBO, LEM5, and LEM10 treatment groups, respectively, during the PBO-controlled period of Study 303).⁶ When adjusted by duration of exposure, overall incidence and rates (subjects per patient-year) of TEAEs related to abuse potential were 0.2, 0.3, and 0.4 for PBO, LEM5, and LEM10, respectively. When adjusted by duration of exposure, the overall rates (events per patient-year) of TEAEs related to abuse potential were 0.3, 0.5, and 0.6 for PBO, LEM5, and LEM10, respectively, with overall rates higher for LEM5 and LEM10 compared with PBO.⁷

Lemborexant binds selectively to orexin-1 and orexin-2 receptors with high affinity, with no evidence of off-target activity at receptors known to be associated with abuse such as dopamine or GABA_A receptors.² In addition, LEM tablets are not readily manipulated for the purposes of intravenous administration (data on file) owing to limited solubility in water. In a pooled analysis of the 2 pivotal phase 3 studies, there was no evidence of abuse or diversion of study medication during clinical development.^{4,6,7}

In nonclinical testing, LEM was not associated with physical dependence, reinforcing effects, or cross-generalization to zolpidem (ZOL).^{7,8} No evidence of physical dependence was observed in Sprague-Dawley rats following 28-day dosing with LEM at doses of up to 600 mg/kg per day. In studies with rhesus monkeys, no active self-administration or gross behavioral changes that suppressed lever pressing were observed during the self-administration period with LEM, and LEM had no reinforcing effect on intravenous self-administration. In a drug discrimination study in rats, LEM, at doses up to 1000 mg/kg, did not cross-generalize to the ZOL (3 mg/kg) training stimulus, whereas SUV demonstrated partial generalization to ZOL as previously reported.^{2,7,9}

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Two previous studies have evaluated the abuse potential of the DORAs SUV and almorexant among recreational drug users.^{10,11} In each of these studies, ZOL differed significantly from PBO on a measure of drug-liking, establishing the validity of each study. SUV (at doses of 40, 80, and 150 mg) and almorexant (200, 400, and 1000 mg) differed significantly from PBO for drug-liking, indicating drug abuse potential. Almorexant 1000 mg and all doses of SUV displayed similar drug-liking to ZOL, but less drug-liking was observed versus ZOL for almorexant 200 and 400 mg.^{9,10}

ZOL and SUV were included in this study as positive controls with known drug-liking, after consultation with the FDA. ZOL was selected as it has been commonly used as a positive control; SUV was added because it shares the same mechanism of pharmacologic action as LEM. Both ZOL and SUV have known abuse potential.¹⁰⁻¹³

METHODS

Study E2006-A001-103 (Study 103; NCT03158025) was a single-center, single-dose, randomized, double-blind, PBO- and active-controlled, 6-way, crossover study conducted from April 19, 2017, to July 4, 2018, in Toronto, Ontario, Canada. The study design was consistent with guidelines of the US FDA for the assessment of abuse potential in humans.³ The protocol and informed consent form were approved by both Health Canada and an institutional review board, and the study adhered to Good Clinical Practice guidelines and the Declaration of Helsinki.

Objectives

The primary objective of this study was to evaluate the abuse potential of single oral daytime doses of LEM compared with PBO in healthy, nondependent, recreational sedative users as determined by mean maximum (peak) effect (E_{max}) for “at this moment” drug-liking.

Secondary objectives of this study were to confirm the abuse potential of ZOL and SUV versus PBO as determined by the E_{max} for “at this moment” drug-liking (to establish study validity), to assess the abuse potential of LEM compared with ZOL and SUV as determined by E_{max} for “at this moment” drug-liking, and to evaluate the safety and tolerability of LEM compared with ZOL, SUV, and PBO.

Key secondary endpoints of cognitive performance of subjects in this study receiving LEM compared with ZOL, SUV, or PBO were also examined as a part of the assessment of the potential for drug abuse for LEM and are described in a separate article.

Subjects

Subjects were healthy men and women 18 to 55 years of age who had body mass index of 18 to 33 kg/m² and weighed at least 50 kg. Each subject was a current sedative user who had used sedatives (eg, ZOL, benzodiazepines) for recreational (nontherapeutic) purposes (ie, for psychoactive effects) at least 5 times in the past year and at least once in the 12 weeks before screening. Subjects were required to be able to discriminate both SUV 40 mg and ZOL 30 mg from PBO on the drug-liking visual analog scale (VAS), show consistent responses on other subjective drug effect measures, and to tolerate study treatment (eg, no episodes of vomiting within the first 3 hours postdose, no unarousable sedation within 4 hours postdose) during the qualification phase. Subjects were excluded if they met the criteria for substance or alcohol dependence in the past 2 years, had ever been in a substance or alcohol rehabilitation program, or had clinically significant illness

or certain medical disorders. A complete list of enrollment criteria is available on clinicaltrials.gov.

Study Design and Treatment

This was a single-dose, randomized, double-blind, crossover study with 3 phases: a qualification phase, a treatment phase, and a follow-up phase (Fig. 1). Subjects were assigned to treatment sequences based on a computer-generated randomization scheme according to a Williams' square design. The following treatments were administered orally during both the qualification and treatment phases: PBO, ZOL immediate release 30 mg, SUV 40 mg (SUV); and in the treatment phase, LEM10, LEM 20 mg (LEM20), and LEM 30 mg (LEM30).

A 40-mg dose of SUV was chosen as the most appropriate to produce adequate abuse-related responses without exposing subjects to unwanted AEs; the 30-mg dose of ZOL was selected for similar reasons.¹⁰ The approved starting dose of SUV for insomnia is 10 mg, with a maximum of 20 mg for adults and 5 mg and 16 mg for the elderly.¹² Approved doses of ZOL immediate release are 5 mg for women and elderly and 5 mg to 10 mg for adult men.¹⁴ The maximum recommended dose of LEM for treatment of insomnia is 10 mg daily.¹⁵ A range of LEM doses were evaluated that were known to be well tolerated and included both a therapeutic dose (10 mg) and 2 supratherapeutic doses (20 and 30 mg), as recommended by the FDA guidance.

Study drug was administered in the morning following an overnight fast of at least 8 hours on designated treatment days (days 1, 4, and 7 during the qualification phase and day 1 during the treatment phase). During the qualification phase and treatment phase, subjects and study personnel were blinded to the treatment codes. Unblinding procedures for the treatment phase were initiated after all assessments were completed on day 10 for the last subject.

All nonstudy medications taken by any subject (including over-the-counter) starting from the day of informed consent until the completion of the final visit of the follow-up stage were recorded as concomitant medication, which were prohibited unless prescribed by investigators to treat clinical events. Concomitant medications could be exempted by the investigators and the sponsor, if it was determined that the medication would be unlikely to affect the study results or subject safety (eg, topical medications).

The purpose of the qualification phase was to confirm the subject was able to distinguish ZOL and SUV versus PBO. During this phase, subjects received a single oral dose of ZOL 30 mg, SUV 40 mg, or PBO in a randomized, double-blind, double-dummy, 3-period crossover manner under fasting conditions. Subjects were required to distinguish ZOL 30 mg and SUV 40 mg from PBO on the “at this moment” drug-liking VAS, defined as a ≥ 15 -point peak (E_{max}) increase for drug-liking in response to ZOL and SUV relative to PBO following drug administration. In addition, on the “at this moment” drug-liking VAS, the subject must have indicated a peak score of ≥ 65 in response to ZOL and SUV and an acceptable peak PBO response of 40 to 60. Treatments were separated by 3 days, and subjects remained in the clinic for 10 days. Subjects who could successfully discriminate and reported they liked ZOL and SUV versus PBO during the qualification phase, and tolerated study treatment, were eligible for randomization into the treatment phase.

The treatment phase lasted for at least 74 days and consisted of 6 in-clinic treatment periods of 4 days each. Treatments (PBO, ZOL, SUV, LEM10, LEM20, and LEM30) were administered in a triple-dummy fashion, and each treatment period was separated by a washout interval of at least 14 days. The follow-up phase

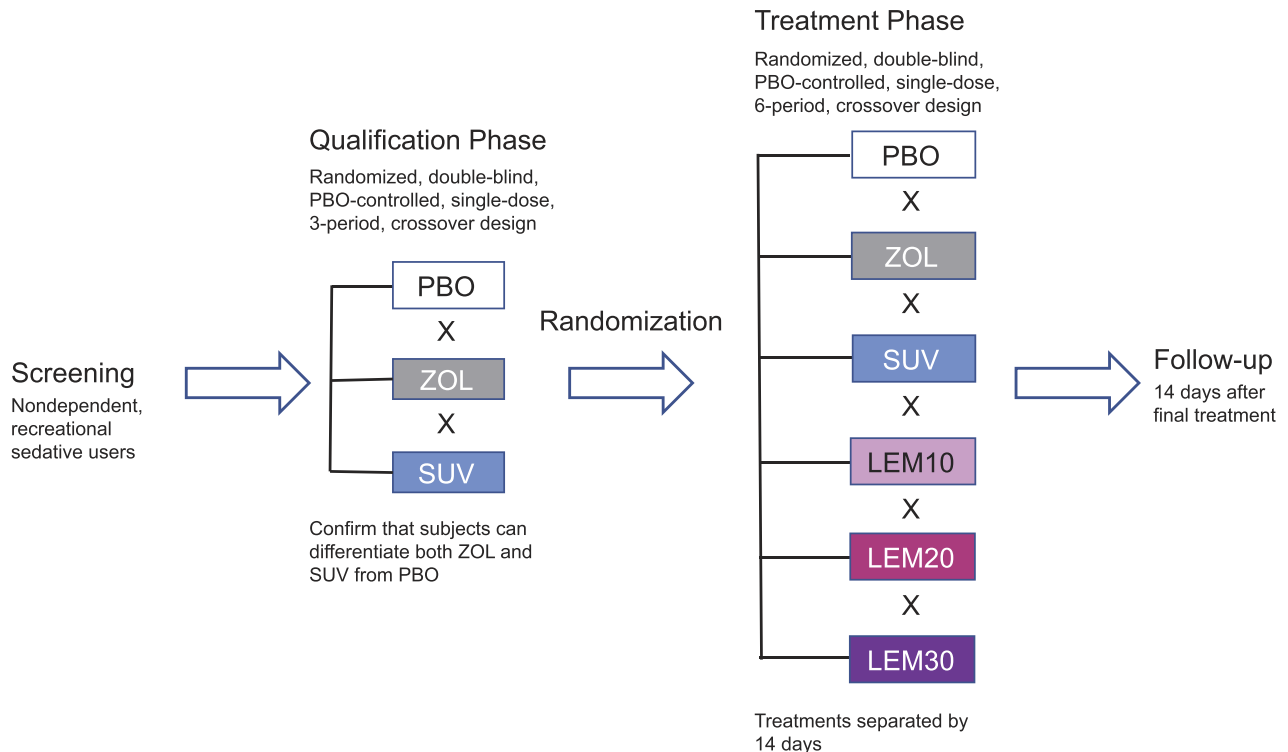


FIGURE 1. Study design. PBO, placebo; ZOL, zolpidem 30 mg; SUV, suvorexant 40 mg; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg.

consisted of 1 visit approximately 14 days after the last study drug administration or at the time of early study discontinuation.

Overview of Outcome Measures

Demographic characteristics evaluated in this study included age, sex, race, and body mass index. The primary drug abuse outcome measure was the VAS for “at this moment” drug-liking. Key secondary endpoints were the overall drug-liking VAS, take-drug-again VAS, high VAS, and good-drug-effects VAS. Additional secondary endpoints included hypothetical subjective drug value (SDV), stoned VAS, bad-effects VAS, and any-effects VAS. Overall drug-liking VAS, take-drug-again VAS, and SDV were measured at least 12 hours after drug administration and were considered global drug effects. Good-effects VAS, stoned VAS, and high VAS were considered to measure positive effects, and the bad-effects VAS was considered to reflect a negative drug effect. Sedation endpoints included alertness/drowsiness VAS, Addiction Research Center Inventory for the pentobarbital-chlorpromazine-alcohol group (ARCI PCAG), and observer’s assessment of alertness/sedation (OAA/S).

Key secondary endpoints also included assessments of the cognitive performance of study subjects following treatment with 10-, 20-, and 30-mg doses of LEM compared with PBO, ZOL, and SUV. These assessments comprised psychomotor evaluations (Choice Reaction Time and Diverted Attention Test assessments) following study drug administration that were performed as part of the primary goal of Study 103 to evaluate LEM abuse potential. The details and results of these assessments are described elsewhere.

The following parameters were evaluated for each pharmacodynamic outcome measure, as appropriate: E_{max} , minimum (peak

effect (E_{min}), maximum change from baseline, and minimum change from baseline. These parameters were assessed over all observations for each measure (between 3 and 13 observations during the 48 hours after study drug administration).

Safety outcome measures included TEAEs, clinical laboratory evaluations, vital signs, electrocardiograms, and physical examinations. Treatment-emergent AEs related to drug abuse potential, including AEs specific to central nervous system—depressant effects, stimulation and anxiety symptoms, perceptual disturbances/psychomimetic effects, mood disorders and disturbances, and mental and cognitive impairment, were prespecified and analyzed.

Description of Pharmacodynamic Outcome Measures

Nine pharmacodynamic measures were formatted as VASs, which were scored as an integer from 0 to 100. Certain VAS measures (“at this moment” drug-liking, overall drug-liking, take-drug-again, alertness/drowsiness) were administered as bipolar measures, with the neutral point equaling 50 and labeled with an anchor such as “neither like nor dislike.” Bipolar scales also had specific anchors at 0 and 100, that is, “strong disliking” and “strong liking,” respectively, for drug-liking and overall drug-liking, or “very drowsy” and “very alert” for alert/drowsiness. The key wording of the VAS measures was largely similar to measures in previous abuse potential studies of DORAs^{10,11} (Supplemental Materials, Table S1, <http://links.lww.com/JCP/A813>). The remaining VASs (good effects, bad effects, any effects, high, and stoned) were administered as unipolar measures, with anchors such as “not at all” (0) and “extremely” (100). The “at this moment” drug-liking, good effects, stoned, high, bad effects, alertness/drowsiness, and any-effects VAS measures were administered at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours after study drug

administration. In addition, the stoned, high, and alertness/drowsiness VASs were administered predose. The overall drug-liking and take-drug-again VAS measures were administered at 12, 24, and 48 hours after study drug administration. E_{\max} or E_{\min} was evaluated for each VAS measure as appropriate (based on the direction of the measure that indicated a stronger effect).

The hypothetical SDV measure^{16,17} involved a series of independent, theoretical, forced choices between the drug administered and different monetary values. The task started at the geometric mean of the range of possible values from \$0.25 to \$50.00, rounded up to the nearest 25 cents. Subjects were asked to choose between receiving another dose of the drug to take home or an envelope containing a specified amount of money. (Subjects did not receive either the drug or the money described in the choices.) Depending on the answer to each question, the monetary value in the next question was either higher or lower. At the end of the procedure (generally 6 questions total), the procedure estimated the crossover point at which a subject was indifferent between choosing the drug and choosing money. The SDV measure was administered at 12, 24, and 48 hours after study drug administration. The E_{\max} of the SDV was also evaluated.

The ARCI PCAG scale^{18–20} measures sedating and intoxicating effects. This scale was originally developed at the Addiction Research Center (Intramural Research Program of the US National Institute on Drug Abuse) based on the differentiating and dose-related sedating and intoxicating effects that were produced by the administration of pentobarbital, chlorpromazine, and alcohol.^{18,19} The ARCI PCAG measure was administered at 1, 2, 4, and 8 hours after study drug administration. The E_{\max} of the ARCI PCAG score was also evaluated. The OAA/S scale²¹ measures level of alertness in subjects who are sedated and includes categories for responsiveness, speech, facial expression, and eyes. The scale is scored as a composite score, defined as the lowest score in any 1 of the 4 assessment categories, and a sum

score, calculated as the total of the scores in the 4 assessment categories. Lower scores indicate greater sedation. The OAA/S scale was administered predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 hours after study drug administration. The E_{\min} of the OAA/S scale score was also evaluated. Subjects were roused if they fell asleep during a scheduled assessment following instructions included in the OAA/S assessment.

Treatment Phase Analysis

During the treatment phase, 3 hypotheses were tested for the primary and key secondary endpoints. A description of the structure of the analyses used with details of the 3 hypotheses is provided in the Supplemental Methods, <http://links.lww.com/JCP/A813>.

Statistical Analyses

Pharmacodynamic analyses were performed in the completers analysis set, defined as subjects who received all study treatments and completed all treatment periods in the treatment phase and had at least 1 “at this moment” drug-liking VAS score within 2 hours of the estimated time to maximum plasma drug concentration for each treatment, regardless of protocol deviations.

Safety analyses were performed in the safety analysis set, defined as subjects who received at least 1 dose of study drug during the treatment phase and had at least 1 postdose safety assessment.

For each endpoint, the mixed-effects model included treatment, period, and treatment sequence as fixed effects and subject nested within treatment sequence as a random effect, in accordance with FDA guidelines.³ As necessary, first-order carryover effects and baseline (predose) measurements were included in the model. Least squares means, 95% confidence intervals, and *P* values for treatment differences were derived from the mixed-

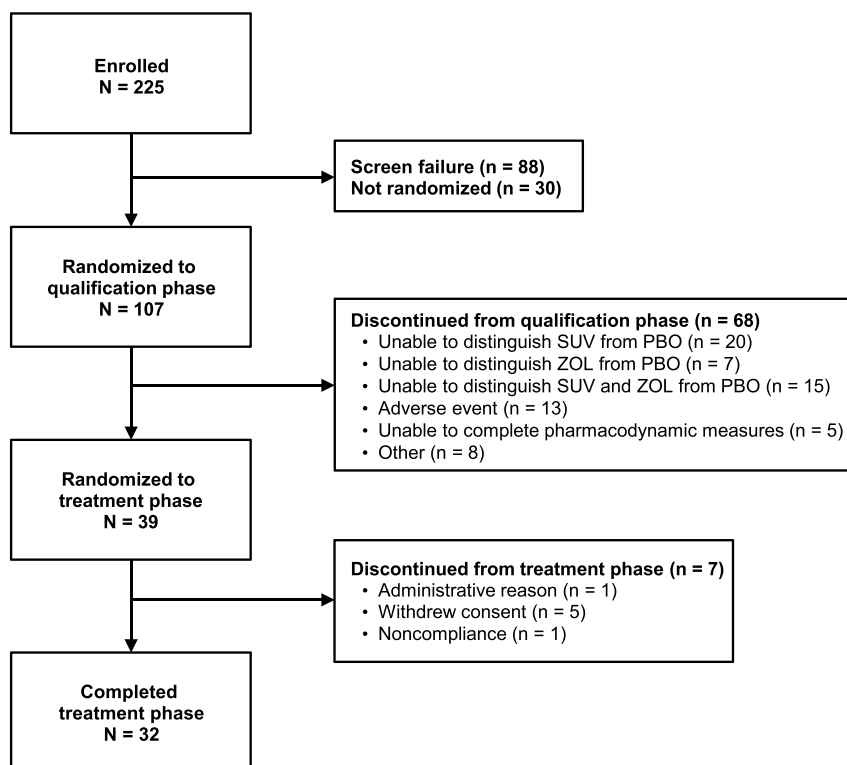


FIGURE 2. Subject disposition. PBO, placebo; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.

effects models. *P* values were provided for the effects and the contrasts. Pharmacodynamic endpoints were analyzed using models, if the residuals from the model were normally distributed. If the residuals from the mixed model were not normally distributed, paired *t* tests were used to assess mean treatment differences, if the distribution of paired differences was normal or symmetric. If paired differences were not normally distributed, the Wilcoxon signed rank test was used to assess median treatment differences. Details of the statistical method used to analyze each outcome measure are provided in the Supplemental Methods, <http://links.lww.com/JCP/A813>. Multiple comparison adjustments were not made.

In the assessments of the primary and key secondary endpoints, for comparisons of LEM versus PBO, *P* > 0.05 indicates that LEM and PBO are significantly different. This is a result of the hypothesis testing structure. For all other comparisons of the primary and key secondary endpoints and for all other endpoints, *P* < 0.05 indicates a statistically significant difference.

RESULTS

Qualification Phase: Subject Disposition and Findings

A total of 225 individuals were screened, of which 88 were screen failures, and a further 30 passed screening but were not randomized into the qualification phase. Of the 107 subjects randomized into the qualification phase (Fig. 2), 35 (32.7%) were unable to distinguish SUV 40 mg from PBO with a margin of 15 points on the “at this moment” drug-liking VAS, and 22 (20.6%) were unable to distinguish ZOL 30 mg from PBO (Fig. 2; these figures include 15 subjects who were unable to distinguish either of the positive controls from PBO). In total, 42 subjects (39.3%) were discontinued because they could not distinguish one or both of the positive controls from PBO at the required margin of 15 points on the drug-liking VAS.

TABLE 1. Baseline Characteristics (Safety Analysis Set)

Parameter	N = 39
Age, y	
Mean (SD)	36.0 (8.6)
Median (range)	36.0 (18–50)
Sex, n (%)	
Male	30 (76.9)
Female	9 (23.1)
Race, n (%)	
White	29 (74.4)
Black or African American	4 (10.3)
Asian	2 (5.1)
American Indian or Alaskan Native	1 (2.6)
Other	3 (7.7)
BMI, mean (SD), kg/m ²	25.5 (2.7)
Recreational sedative use in past year, n (%)	
Depressants	39 (100)
Opioids and morphine derivatives	25 (64.1)
No. times sedatives* used recreationally in past year, mean (SD)	83.5 (70.5)

*Sedatives include “depressants” and “opioids and morphine derivatives.”
BMI, body mass index.

Overall, 68 subjects (63.6%) were discontinued during the qualification phase. Among 32 eventual qualification completers, mean drug-liking VAS E_{\max} values for ZOL 30 mg and SUV 40 mg during the qualification phase were 89.0 (range, 67–100) and 89.8 (range, 68–100), respectively, compared with 50.4 (range, 50–52) for PBO. This resulted in a mean difference from PBO of 38.6 (range, 17–50) and 39.4 (range, 18–50) points for ZOL and SUV, respectively.

During the qualification phase, 13 subjects (12.1%) were discontinued because of AEs, including 10 subjects who experienced nausea, vomiting, or retching. Five subjects (4.7%) were unable to complete pharmacodynamics measures, and 8 subjects (7.5%) discontinued for other reasons.

Treatment Phase: Subject Disposition and Characteristics

Thirty-nine subjects continued from the qualification phase to the treatment phase (safety analysis set; Fig. 2). During the treatment phase, 7 subjects withdrew early (none owing to AEs), and 32 subjects completed the treatment phase (completer analysis set). The 39 subjects in the safety analysis set had a mean age of 36.0 (SD, 8.6) years; 30 (76.9%) were male; 29 (74.4%) were White; and subjects had used sedatives recreationally a mean of 83.5 (SD, 70.5) times in the previous year (Table 1).

Study Validity

The difference in mean “at this moment” drug-liking VAS E_{\max} values was compared between the positive controls (ZOL 30 mg and SUV 40 mg) and PBO. When applying a validation margin of 15, the differences in mean E_{\max} values for the positive controls and PBO, were not significantly different (Fig. 3; Supplemental Materials, Table S2, <http://links.lww.com/JCP/A813>). When applying a validation margin of 11, mean E_{\max} values for ZOL and SUV were significantly greater compared with PBO, thereby confirming study validity.

Primary Endpoint

For each LEM dose, mean “at this moment” drug-liking E_{\max} values were significantly greater than values for PBO, as shown in Figure 3B (Supplemental Materials, Table S2, <http://links.lww.com/JCP/A813>). On this measure, LEM was not significantly different from ZOL 30 mg or SUV 40 mg. For all active agents (ZOL, SUV, and LEM), “at this moment” drug-liking values rose rapidly postdose, reached E_{\max} (peak) in the drug-liking range of the scale at 1.5 to 3 hours, and then declined over time to reach a stable level at approximately 8 hours after drug administration (Fig. 3B). Mean scores for PBO remained neutral (close to 50 points) throughout the assessment time course. Overall, the results do not show evidence of a dose response for LEM (higher doses of LEM having a higher potential for abuse) (Fig. 3).

Secondary Endpoints

For each of the key secondary endpoints (overall drug-liking VAS, take-drug-again VAS, high VAS, and good-drug-effects VAS), the mean E_{\max} for each active agent (ZOL 30 mg, SUV 40 mg, and all doses of LEM) was significantly greater than the E_{\max} for PBO (Table 2). For each key secondary endpoint, there were no significant differences between any dose of LEM compared with ZOL 30 mg or SUV 40 mg. Similarly, for the SDV, mean E_{\max} values were significantly greater for all active agents compared with PBO, but there were no

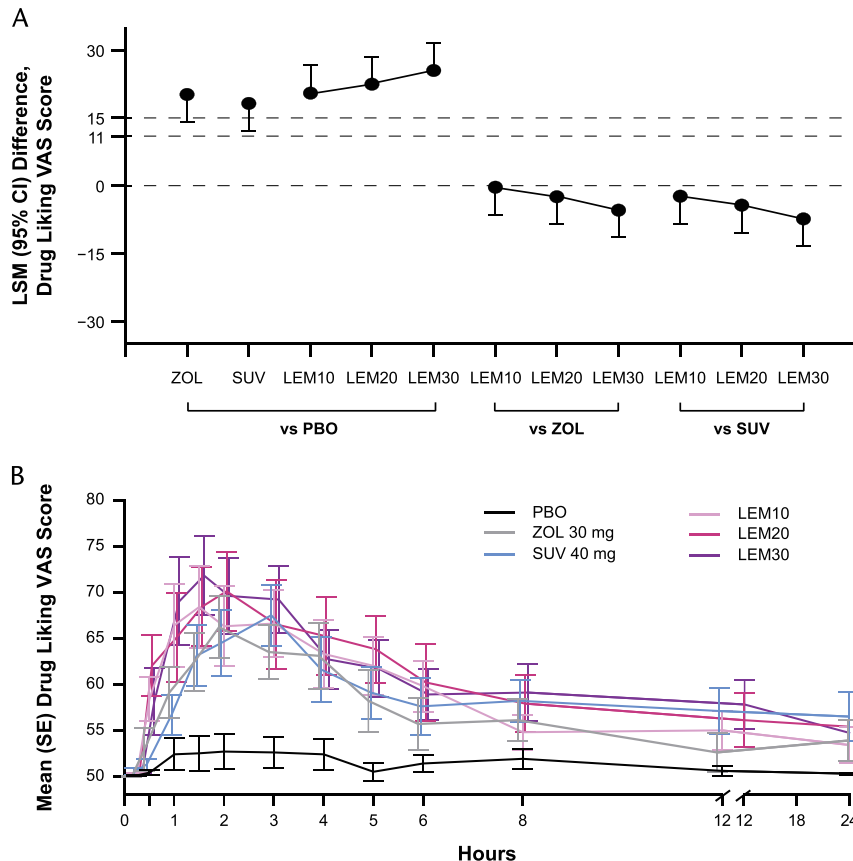


FIGURE 3. “At this moment” drug-liking VAS response to PBO, ZOL, SUV, and LEM. The primary endpoint was maximum (peak) effect (E_{max}). A, LSM (95% CI) differences in E_{max} between treatments. Validation margins of 11 and 15 points for the difference in means between the positive controls (ZOL and SUV) and PBO are indicated. B, Mean (SE) drug-liking VAS score over time for each treatment group. CI, confidence interval; E_{max} , maximum (peak) effect; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; LSM, least squares mean; PBO, placebo; SE, standard error; SUV, suvorexant 40 mg; VAS, visual analog scale; ZOL, zolpidem 30 mg.

significant differences for any dose of LEM compared with ZOL or SUV (Table 2).

For the additional endpoints stoned VAS, bad-effects VAS, and any-effects VAS, each active agent had a significantly higher mean E_{max} value (stronger effect) than PBO (Table 2). For each of these 3 endpoints, each dose of LEM had a significantly stronger effect than SUV 40 mg. In addition, LEM30 had a significantly stronger effect for any-effects VAS than ZOL 30 mg, and LEM10 had a lower mean E_{max} value (weaker effect) for bad-effects VAS than ZOL.

For endpoints related to sedation (alertness/drowsiness VAS, ARCI PCAG, and the OAA/S composite and sum scores), each active agent caused significantly greater sedative effects than PBO (Table 2). Each dose of LEM caused significantly stronger sedative effects than ZOL 30 mg based on the alertness/drowsiness VAS, but significantly weaker sedative effects than ZOL based on the OAA/S composite and sum scores. Based on the alertness/drowsiness VAS, ARCI PCAG, and OAA/S composite score, LEM20 and LEM30 caused significantly greater sedative effects than SUV 40 mg (Table 2). Values for findings for secondary endpoint measures are shown in Supplemental Materials, Table S3, <http://links.lww.com/JCP/A813>.

Safety

Incidence of TEAEs during the treatment phase was greater with ZOL 30 mg, SUV 40 mg, and all doses of LEM compared

with PBO (Table 3). The most common TEAE was somnolence, which was experienced by >85% of subjects after receiving each active treatment. This finding was expected, because LEM, SUV, and ZOL are sleep-promoting drugs that were administered in the morning. After receiving ZOL, 14.3% of subjects experienced dizziness, and 28.6% experienced diplopia. Headache was experienced by >14% of subjects receiving ZOL, LEM10, and LEM20. Otherwise, no TEAE was experienced by $\geq 12\%$ of subjects after receiving any treatment (Table 3).

Sleep paralysis was noted only for subjects receiving SUV or LEM. Three subjects experienced sleep paralysis more than once, during different treatment conditions. One subject experienced sleep paralysis with both SUV and LEM10; one with LEM10, LEM20, and LEM30; and one with LEM10 and LEM20. Among TEAEs potentially associated with drug abuse potential, only somnolence and dizziness occurred among >10% of subjects following any active treatment. Euphoric mood occurred in 3 different subjects (8.1%) receiving LEM10, 2 additional subjects (5.7%) receiving ZOL, and 2 additional subjects (5.7%) receiving LEM30.

One subject experienced severe TEAEs of cataplexy and somnolence after receiving ZOL. Otherwise, no subjects experienced severe TEAEs. The event of cataplexy and TEAEs potentially related to cataplexy were reviewed by an independent adjudication committee that comprised experts; none was adjudicated

TABLE 2. Summary of Direction of Between-Treatment Differences of Means for Key Secondary, Additional, and Sedation Endpoints (Completer Analysis Set)

	ZOL- PBO*	SUV- PBO*	LEM10- PBO†	LEM20- PBO†	LEM30- PBO†	ZOL- LEM10‡	ZOL- LEM20‡	ZOL- LEM30‡	SUV- LEM10‡	SUV- LEM20‡	SUV- LEM30‡
Key secondary endpoints [§]											
Overall drug-liking VAS E_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
Take-drug-again VAS E_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
High VAS E_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
Good effects VAS E_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
Additional endpoints [§]											
SDV E_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
Stoned VAS E_{max}	>	>	>	>	>	NS	NS	NS	<	<	<
Bad effects VAS E_{max}	>	>	>	>	>	>	NS	NS	<	<	<
Any effects VAS E_{max}	>	>	>	>	>	NS	NS	<	<	<	<
Sedation endpoints											
Alertness/drowsiness VAS E_{min}	<	<	<	<	<	>	>	>	>	>	>
ARCI PCAG [¶] E_{max}	>	>	>	>	>	NS	NS	NS	NS	<	<
OAA/S composite score [#] E_{min}	<	<	<	<	<	<	<	<	NS	>	>
OAA/S sum score [#] E_{min}	<	<	<	<	<	<	<	<	NS	NS	NS

> Indicates between-treatment difference in means is positive and statistically significant; < indicates between-treatment difference in means is negative and statistically significant; NS indicates difference is not statistically significant.

*For positive control (ZOL and SUV) versus PBO comparisons for key secondary endpoints, hypothesis tests were constructed as follows: $H_0: \mu_C - \mu_P \leq 11$ vs $H_A: \mu_C - \mu_P > 11$, where C = positive control (ZOL and SUV) and P = PBO. For additional endpoints, comparisons tested the null hypothesis that the difference of the means between treatment groups is zero.

†For LEM versus PBO comparisons for key secondary endpoints, hypothesis tests were constructed as follows: $H_0: \mu_T - \mu_P \geq 11$ versus $H_A: \mu_T - \mu_P < 11$, where T = test drug (LEM) and P = PBO. For additional endpoints, comparisons tested the null hypothesis that the difference of the means between treatment groups is zero.

‡For LEM versus positive control (ZOL and SUV) comparisons for key secondary endpoints, hypothesis tests were constructed as follows: $H_0: \mu_C - \mu_T \leq 0$ versus $H_A: \mu_C - \mu_T > 0$, where C = positive control (ZOL and SUV) and T = test drug (LEM). For additional endpoints, comparisons tested the null hypothesis that the difference of the means between treatment groups is zero.

§For the key secondary and additional endpoints, higher scores on each measure indicate a larger effect.

||For the alertness/drowsiness VAS, lower scores indicate greater drowsiness. For example, peak drowsiness was less (E_{min} was larger) for PBO versus active treatments.

¶For the ARCI PCAG scale, higher scores indicate greater sedation.

#For the OAA/S composite and sum scales, lower scores indicate greater sedation.

ARCI PCAG, Addiction Research Center Inventory, pentobarbital-chlorpromazine-alcohol group; E_{max} , maximum (peak) effect; E_{min} , minimum (peak) effect; LEM, lemborexant; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; NS, not significant; OAA/S, observer's assessment of alertness/sedation; PBO, placebo; SUV, suvorexant 40 mg; VAS, visual analog scale; ZOL, zolpidem 30 mg.

TABLE 3. Summary of TEAEs During the Treatment Phase (Safety Analysis Set)

	PBO (n = 36)	ZOL (n = 35)	SUV (n = 34)	LEM10 (n = 37)	LEM20 (n = 34)	LEM30 (n = 35)
General category of events, n (%)						
Any TEAE	14 (38.9)	34 (97.1)	31 (91.2)	35 (94.6)	33 (97.1)	34 (97.1)
Any TEAE of abuse potential	8 (22.2)	34 (97.1)	30 (88.2)	35 (94.6)	32 (94.1)	34 (97.1)
TEAEs occurring in >3 subjects in any active treatment group, n (%)						
Somnolence*	6 (16.7)	30 (85.7)	29 (85.3)	34 (91.9)	30 (88.2)	34 (97.1)
Sleep paralysis	0	0	1 (2.9)	3 (8.1)	4 (11.8)	4 (11.4)
Dizziness*	0	5 (14.3)	1 (2.9)	3 (8.1)	2 (5.9)	4 (11.4)
Muscular weakness	0	0	0	0	2 (5.9)	4 (11.4)
Diplopia	0	10 (28.6)	1 (2.9)	2 (5.4)	0	4 (11.4)
Headache	3 (8.3)	5 (14.3)	3 (8.8)	6 (16.2)	6 (17.6)	3 (8.6)
Nausea	0	4 (11.4)	0	0	1 (2.9)	0
Vomiting	0	4 (11.4)	0	2 (5.4)	0	0

*TEAE related to drug abuse potential.

LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; PBO, placebo; SUV, suvorexant 40 mg; TEAE, treatment-emergent adverse event; ZOL, zolpidem 30 mg.

as cataplexy. There were no serious TEAEs or deaths, and no subject discontinued the study drug during the treatment phase owing to TEAEs.

DISCUSSION

All doses of LEM demonstrated abuse potential versus PBO among healthy, nondependent, recreational sedative users who previously were able to distinguish both ZOL and SUV from PBO during the qualification phase. This finding is consistent with the findings with SUV and almorexant in earlier studies.^{10,11} However, subjects in this study differ from those in the almorexant and SUV studies in that the subjects in the studies of SUV and almorexant were not selected based on their ability to distinguish another DORA from PBO with a robust 15-point increase in drug-liking. Thus, this increased the likelihood that LEM would produce similar liking scores unless its subjective effects related to liking were different. The findings also support the rationale for similar Controlled Substances Act scheduling for LEM and SUV.^{10,11}

On the primary and key secondary measures indicating abuse potential, the abuse potential profiles for all doses of LEM were similar to each other and to the profiles observed for ZOL and SUV. Some differences between LEM and SUV were observed. On a secondary measure of self-reported feeling “stoned,” elevated scores for LEM were reported compared with SUV. Lemborexant was also associated with increased “bad” and “any” effects compared with SUV, irrespective of dose level. As these effects were not seen to be dose dependent (they were seen at therapeutic doses of LEM as well as supratherapeutic doses), difference in effects compared with SUV may be due to LEM and SUV having different affinity for orexin receptors. Comparison between SUV and ZOL was not an objective of this study and is limited by the fact that only 1 dose of SUV was used in this study.

Lemborexant was generally well tolerated, and TEAEs observed for LEM were consistent with the known AE profile. Severe AEs occurred in only 1 subject, after administration of ZOL. There were no serious AEs during the study. Doses of SUV and ZOL in this study were 2 to 3 times the highest approved dosage for treatment of insomnia, respectively, as is typical for human abuse potential studies.³ Similarly, LEM was tested at doses ranging from the

highest approved therapeutic dose and up to 3 times the highest approved dose of 10 mg. At these high doses, it is expected that somnolence would be experienced by most subjects when receiving active treatment, especially following morning dosing.²² Sleep paralysis was observed only with DORAs and not with ZOL. This is most likely related to differences in mechanism of action of different classes of sleep-promoting agents. Three subjects experienced sleep paralysis during more than 1 active treatment condition, indicating that some individuals may be more susceptible to this adverse effect when taking DORAs.

The higher proportion of men (76.9%) than women in this study is common for studies of drug abuse potential.¹⁰ Therefore, the study population may not have been representative of all recreational sedative users. The relatively high rates of subject exclusion compared with earlier studies^{10,11} suggest that the present study approach may have increased sensitivity to discriminate across the drugs. Forty-two subjects (39.3%) were discontinued in the qualification phase because they could not distinguish one or both of the positive controls (ZOL and SUV) from PBO at the required margin of 15 points on the drug-liking VAS. More subjects were unable to differentiate SUV from PBO (35 subjects) than ZOL from PBO (22 subjects) during the qualification phase. This pattern may be related to differences in relative abuse potential of DORAs as a class, compared with ZOL, and suggests that there may be differences in abuse potential between the 2 drug classes that may be detectible in a study of different design (eg, forced choice). Because of the high rates of discontinuation in the qualification phase, findings for this study are limited to the portion of enrolled subjects who could distinguish and like both ZOL and SUV from PBO. Individuals who reached the treatment phase may therefore have higher capability of liking and distinguishing between active and inactive treatment compared with all recreational sedative users.

The higher failure rates among subjects with a history of drug abuse to distinguish between DORAs and PBO during screening are consistent with earlier preclinical research in rats and rhesus monkeys that indicated a relatively low risk of abuse potential for DORAs.^{7,8} No euphoria was reported at therapeutic doses of LEM during the pivotal phase 3 trials,⁷ and euphoric mood was experienced by <10% of subjects receiving any dose of LEM in this study. Future research will be required to distinguish ZOL and drugs of its class from DORAs in abuse potential.

The overall assessment of abuse potential of LEM, with emphasis given to this human abuse potential study, contributed to the FDA recommendation of placement by the US Drug Enforcement Administration in Schedule IV of the Controlled Substances Act.³ Drugs in Schedule IV are considered to have a relatively low potential for abuse and a low risk of dependence as compared with Schedule III barbiturates, phenacyclidine, and ketamine.²³ However, patients with a history of drug abuse may be at a higher risk of misusing LEM and should therefore be followed carefully by their clinicians; this caution is also found in the approved labeling for SUV and ZOL.¹⁵ The absence of demonstrated physical dependence/withdrawal and other differences in the pharmacology of LEM compared with ZOL and other benzodiazepines suggests the possibility that the real-world abuse potential of LEM will be lower. However, this must be demonstrated in postmarketing studies. Without this real-world evidence, it should be assumed that the abuse potential of LEM is similar to that of other Schedule IV drugs. Postmarketing studies will be important to determine if real-world rates of abuse and/or problem use of LEM are similar to those observed with benzodiazepines.²³

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DATA AVAILABILITY STATEMENT

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

AUTHOR DISCLOSURE INFORMATION

I.L., N.H., J.A., G.F., L.R., and M.M. are employees of Eisai Inc. At the time of the study, B.S. was an employee of Syneos Health; B.S. is a current employee of Altasciences; J.H. is an employee of Pinney Associates through which he provided consulting support to Eisai on LEM.

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