Acute Cognitive Effects of the Dual Orexin Receptor Antagonist Lemborexant Compared With Suvorexant and Zolpidem in Recreational Sedative Users

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Abstract:

Purpose/Background: As part of a human abuse potential (HAP) study of lemborexant (LEM), the effects of therapeutic (LEM 10 mg), and supratherapeutic doses of LEM 20 mg and LEM 30 mg on cognition and psychomotor performance were compared with placebo (PBO) and supratherapeutic doses of zolpidem (ZOL) 30 mg and suvorexant (SUV) 40 mg. Subjects (n = 32) were healthy, nondependent, recreational sedative users able to discriminate the effects of both SUV and ZOL from PBO on subjective drug measures.

Methods/Procedures: The human abuse potential study was a single-dose, randomized, double-blind, PBO-controlled, 6-way crossover study. Eligible subjects admitted to the treatment phase completed the choice reaction test (CRT) and divided attention test. The CRT included measurements of recognition reaction time (RRT) and motor reaction time.

Findings/Results: Recognition reaction time and mean maximum change from baseline (CFBmax) scores were significantly increased (slower performance) versus PBO for all LEM doses (all P < 0.001), ZOL (P < 0.001), and SUV (P = 0.004), and LEM (all doses) was not statistically different from ZOL or SUV. Motor reaction time and mean CFBmax versus PBO were significantly increased for all LEM doses (all P < 0.001), and ZOL (P < 0.001) and SUV (P < 0.001). All LEM doses showed significantly decreased (better performance) mean CFBmax versus ZOL (all P < 0.001), but not SUV. Notably, all cognitive effects in the CRT and divided attention test were limited to the main treatment phase (up to 8 hours postdose).

Implications/Conclusions: All active doses of LEM, ZOL, and SUV generally increased reaction time and reduced divided attention capabilities versus PBO. However, at therapeutic/supratherapeutic doses, LEM led to significantly less cognitive impairment than supratherapeutic doses of ZOL in some measures.

Key Words: abuse potential, cognitive effects, dual orexin receptor antagonist, lemborexant
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Lemborexant (LEM) is a dual orexin receptor antagonist (DORA) approved for the treatment of insomnia in adults in multiple countries including the United States, Japan, Canada, Australia, and several Asian countries. Significant benefits were reported for LEM for sleep onset and sleep maintenance compared with placebo (PBO) in 2 pivotal phase 3 studies in subjects with insomnia disorder. Study E2006-G000-304 (Study 304; SUNRISE-1; NCT02783729) and Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820). The mechanism of action of LEM, as a DORA, is different from benzodiazepines and z-drugs (ie, zolpidem, eszopiclone/zopiclone, and zaleplon) also used to treat insomnia, as the antagonism of orexin receptors by DORAs suppresses inappropriate wakefulness. In contrast, benzodiazepine hypnogens and z-drugs promote sleep-inducing pathways through a γ-aminobutyric acidergic mechanism of action.

Study E2006-A001-103 (Study 103; NCT03158025), which is presented here, was a phase 1, randomized, double-blind, PBO-controlled, 6-period crossover study with the primary objective to evaluate the abuse potential of single oral daytime doses of LEM (10 mg therapeutic dose [LEM10] and supratherapeutic doses 20 mg [LEM20] and 30 mg [LEM30], a choice of dose range informed by US Food and Drug Administration (US FDA) guidance) compared with PBO in healthy, nondependent, recreational sedative users as determined by peak maximum effect for “at this moment” drug-liking.

The attractiveness of a drug for purposes of abuse, as well as drug safety, can be affected by the ability of a drug to induce changes in cognition or performance and the nature of those changes, as discussed by the US FDA and elsewhere. This approach is an objective way to assess potential psychoactive effects relative to prototypic benzodiazepines approved for treatment of insomnia and the effects associated with intoxication. As part of assessing the potential for abuse of LEM in Study 103, it was therefore important to evaluate the effects of LEM at therapeutic and supratherapeutic doses on cognitive and psychomotor performance. Key secondary endpoints of Study 103 were the choice reaction test (CRT) and the divided attention test (DAT), which assessed the effect on cognitive and psychomotor performance of LEM and supratherapeutic doses of active comparators, the z-drug, zolpidem (ZOL) 30 mg, and the DORA suvorexant (SUV) 40 mg compared with PBO. Suvorexant, as a DORA, was added to this study because it shares the same mechanism of pharmacologic action as LEM and has been previously studied for abuse potential.

Cognitive assessments were also measured at preselected time points during the target therapeutic period (ie, 0.25 to 8 hours postdose), which is the timeframe where LEM is intended to exert a sleep-promoting effect, and in the posttarget or next-day period (8 hours to 24 hours postdose), where any residual drug-related effect is undesirable.

We report here these cognitive function and performance assessments following treatment with therapeutic LEM10 and supratherapeutic doses of LEM20 and LEM30 compared with PBO and supratherapeutic doses of ZOL and SUV in Study 103. Additional endpoints related to abuse potential were also examined in Study 103 and are reported elsewhere along with results from the primary endpoint of drug-liking.
METHODS

The overall design of Study 103 was consistent with the 2017 guidelines of the US FDA for the assessment of abuse liability of central nervous system active compounds in humans,4 the details of which have been previously described.7 The study protocol and informed consent form were approved by an institutional review board, and the study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. All subjects provided written informed consent.

Objectives

The objective of these analyses was to evaluate the effects of therapeutic and supratherapeutic doses of LEM on cognition and performance compared with PBO and supratherapeutic doses of active comparators ZOL and SUV in healthy, nondependent, recreational sedative users. This analysis was an evaluation of key secondary endpoint results from Study 103 and was intended to aid in the understanding of the abuse potential of LEM.

Subjects

A description of subject demographics has been previously reported.7 Briefly, subjects were healthy males and females between 18 and 55 years of age who were current sedative users and had used sedatives (eg, ZOL, benzodiazepines) for recreational purposes (eg, nontherapeutic psychoactive effects) at least once in the 12 weeks before screening and ≥5 times during the previous year.

Subjects were screened for the ability to discriminate both SUV 40 mg and ZOL 30 mg from PBO on subjective drug measures and were able to tolerate study treatment during the qualification phase. Subjects were excluded if they met the criteria for substance or alcohol dependence in the past 2 years or had ever been in a program for substance or alcohol rehabilitation. A complete list of enrollment criteria is available on clinicaltrials.gov (NCT03158025).

Study Design and Treatment

Study 103 was a single-center, single-dose, randomized, double-blind, PBO-controlled, 6-way crossover study with 3 phases: a qualification phase, a treatment phase, and a follow-up phase. The study was conducted from April 19, 2017, to July 4, 2018 in Toronto, Canada. Further details of the design of Study 103 have been previously described.

For the treatment of insomnia, maximum approved doses for SUV, ZOL immediate release, and LEM are 20 mg, 10 mg, and 10 mg, respectively. Human abuse potential studies typically include doses that are 2 to 3 times the therapeutic dose of test compounds. Therefore, treatments during the qualification and treatment phases (administered orally) were as follows: PBO; ZOL 30 mg; SUV 40 mg; and (in the treatment phase) LEM10, LEM20, and LEM30. Additional rationale for selecting the specific doses of LEM, ZOL, and SUV used in this abuse potential study has been previously described. The study drug was administered in the morning after an overnight fast of at least 8 hours. An approximate 14-day follow-up period occurred immediately after the final study drug administration and concluded with an end of study visit.

Statistical Analyses

Cognition endpoints were analyzed in the completor analysis set, defined as the group of subjects who received all study treatments.
and completed all treatment periods in the main treatment phase as well as had ≥1 primary endpoint assessment (“at this moment” drug-liking VAS score) within 2 hours of the estimated time to maximum plasma concentration (t_{max}) for each treatment, regardless of protocol deviations.

A mixed-effect model was used to analyze cognition endpoints. The model included treatment period, treatment sequence, and first-order carryover effect (where applicable) as fixed effects, baseline (predose) measurements as covariate (where applicable), and subject nested within treatment sequence as a random effect. Least squares means, 95% confidence intervals, standard error, and P values for treatment differences were derived from the mixed-effect model if the normality assumption of the model was met. If the normality assumption of the model was not met, the paired differences from each of the contrasts were tested using a t test (means) if the distribution of the paired differences was normal or by Wilcoxon signed rank test (medians) if the distribution of the paired differences was not normal. Overall treatment effects were assessed using Friedman test.

Safety
Safety analyses were performed in the safety analysis set, defined as subjects who received ≥1 dose of study drug during the main treatment phase and had ≥1 postdose safety assessment as previously described.7 Treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, vital signs, electrocardiograms, and physical examinations were assessed as part of Study 103 and have been previously described.7

RESULTS

Subject Disposition and Characteristics
A total of 225 subjects were screened, from which 107 were randomized to the qualification phase. Of these 107 subjects, 68 (63.6%) discontinued from the qualification phase with 43 of 107 (40.2%) not meeting qualification criteria. Twenty subjects (18.7%) could not discriminate SUV from PBO, and 7 (6.5%) could not discriminate ZOL from PBO; 7 subjects (6.5%) could not discriminate either SUV or ZOL from PBO. Twenty-five of 107 subjects (23.4%) discontinued for other reasons. Thirty-nine subjects (safety analysis set) met the qualification criteria and were randomized into the main treatment phase; 32 subjects (7 discontinued) received and completed all treatments. Subjects in the safety analysis set had a median (range) age of 36.0 (18–50) years, were mostly male (30 of 39 [76.9%]), and White (29 of 39 [74.4%]). Additional details of subject disposition and characteristic have been previously reported.

TABLE 1. Summary of Direction Between-Treatment Differences of Means for Cognitive 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 |
|------------------|---------|---------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Choice RT task   |         |         |           |           |           |           |           |           |           |           |           |
| Recognition RT*  | >       | >       | >         | >         | >         | NS        | NS        | NS        | NS        | NS        | NS        |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Motor RT*        | >       | >       | >         | >         | >         | >         | >         | >         | >         | >         | >         |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Total RT*        | >       | >       | >         | >         | >         | >         | >         | >         | >         | >         | >         |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Percentage correct† | <     | <       | <         | <         | <         | <         | <         | <         | <         | <         | <         |
| CFB_{min}        |         |         |           |           |           |           |           |           |           |           |           |
| Divided attention task |         |         |           |           |           |           |           |           |           |           |           |
| RMS distance from center of road* | >   | >       | >         | >         | >         | >         | >         | >         | >         | >         | >         |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Greatest distance from center of road* | > | >       | >         | >         | >         | NS        | NS        | NS        | <         | <         | <         |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Response latency of correct responses* | > | >       | >         | >         | >         | NS        | NS        | NS        | NS        | NS        | NS        |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| No. false alarms* | >   | NS      | NS        | NS        | NS        | >         | >         | >         | NS        | NS        | NS        |
| CFB_{max}        |         |         |           |           |           |           |           |           |           |           |           |
| Percentage of time over road† | < | <       | <         | <         | <         | <         | <         | <         | <         | <         | <         |
| CFB_{min}        |         |         |           |           |           |           |           |           |           |           |           |
| Percentage of target hits‡ | < | <       | <         | <         | <         | <         | <         | <         | <         | <         | <         |
| CFB_{min}        |         |         |           |           |           |           |           |           |           |           |           |

> indicates that between-treatment difference in means is positive and statistically significant; < indicates that between-treatment difference in means is negative and statistically significant; NS indicates difference is not statistically significant. For each endpoint, comparisons tested the null hypothesis that the difference of the means between treatment groups is zero.

*Smaller CFB is better.

†Less negative CFB (change in percentage correct closer to zero) is better. For example, reduction in percentage correct was less (CFB_{max} was less negative) for PBO versus active treatments.

‡Less negative CFB (closer to zero) is better.

CFB indicates change from baseline; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; NS, not significant; PBO, placebo; RT, reaction time; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.
Choice Reaction Test

For each of the 3 measures of the CRT task, each active agent (ZOL 30 mg, SUV 40 mg, and all doses of LEM) caused a significantly greater reduction in performance from baseline compared with PBO (Table 1). Based on MRT, TRT, and percentage correct, ZOL 30 mg caused a numerically greater reduction in performance compared with all doses of LEM. Based on percentage correct, all doses of LEM caused a greater reduction numerically in performance compared with SUV 40 mg. Findings for LEM versus SUV were generally nonsignificant for the other CRT measures.

Mean CFBmax scores for RRT were significantly greater versus PBO for all LEM doses (all P < 0.001) and for ZOL (P < 0.001) and SUV (P = 0.004). For all doses, LEM was not significantly different compared with ZOL or SUV (Table 2). For MRT, mean CFBmax scores versus PBO were significantly greater for all LEM (all P < 0.001) and for ZOL (P < 0.001) and SUV (P < 0.001). Zolpidem showed statistically significantly greater mean CFBmax (larger mean increase in MRT) scores compared with all doses of LEM (all P < 0.001), but mean CFBmax scores for LEM and SUV were not significantly different (Table 2).

Finally, for TRT, mean CFBmax scores versus PBO were significantly greater for LEM (all P < 0.001) and for ZOL (P < 0.001) and SUV (P < 0.001). Mean CFBmax score for LEM30 was significantly greater compared with SUV (P = 0.025). Zolpidem showed significantly greater mean CFBmax scores compared with all doses of LEM (all P < 0.001) (Table 2).

For the percentage of correct responses, mean CFBmin was significantly greater for all doses of LEM (all P < 0.01) and for ZOL (P < 0.001) and SUV (P < 0.05) compared with PBO. All LEM doses exhibited significantly higher mean CFBmin (smaller decrease in percentage correct) compared with ZOL (all P ≤ 0.001). All doses of LEM exhibited significantly lower mean CFBmin (greater decrease in percentage correct) compared with SUV (all P < 0.05). For LEM, SUV, and ZOL, CFBmin for RRT, TRT, and TRT was observed within 2 hours after drug administration with CFB for all cognitive performance measures and all treatment groups consistently returning to baseline by 8 hours after drug administration (Fig. 1).

Divided Attention Task

For all measures of the DAT except for the number of false alarms, each active agent (ZOL 30 mg, SUV 40 mg, and all doses of LEM) exhibited a significantly greater reduction in performance from baseline compared with PBO (Table 1, Fig. 2). On 4 of the measures: RMS distance from the center of the road, percentage of time over the road, number of false alarms, and percentage of target hits, ZOL 30 mg showed reductions in performance compared with each dose of LEM (Table 1, Fig. 2). On the divided attention task measures, which are RMS distance from center of road, greatest distance from center of road, and percentage of time over road, both LEM20 and LEM30 caused significantly more loss of performance than SUV 40 mg (Table 1, Fig. 2).

For RMS, all doses of LEM exhibited statistically significantly lower mean CFBmax scores compared with ZOL (P = 0.001, P = 0.027, and P = 0.039 for LEM10, LEM20, and LEM30, respectively) indicative of improved motor control. Lemborexant (20 mg) and LEM30 showed significantly higher mean CFBmax scores compared with SUV (P = 0.007 and P = 0.004, respectively), indicative of reduced motor precision (Table 3). Mean CFBmax scores for LEM, ZOL, and SUV were significantly higher compared with SUV. Zolpidem exhibited the quickest and largest postdose increase in RMS distance (Fig. 2A).

Similarly, for greatest distance from the center of the road, where increases indicate greater impairment, mean CFBmin values followed a similar pattern across treatment groups as that observed for RMS distance. Lemborexant (10 mg) showed significantly lower mean CFBmax compared with ZOL (Table 3). Lemborexant (20 mg) and LEM30 showed significantly higher mean CFBmax compared with SUV. Mean CFBmax scores for LEM and the active comparators were significantly higher compared with PBO (Fig. 2B).

All doses of LEM exhibited statistically significant higher CFBmin scores (small decrease in percentage over the road) compared with ZOL for percentage of time over the road. Lemborexant (20 mg) and LEM30 showed significantly lower CFBmin scores compared with SUV. Mean CFBmin values for LEM (33.9% to −35.0%), ZOL (−45.3%), and SUV (−29.9%) were significantly lower compared with PBO (−12.74%) (Table 3). Zolpidem exhibited the quickest and largest postdose decrease in percentage over the road (Fig. 2C).

For response latency of correct responses, where longer times indicate greater impairment, mean CFBmax values followed a similar pattern seen for RMS distance. Mean CFBmax for LEM and the active comparators was significantly higher than PBO; however, there were no significant differences between the active comparators and LEM (Table 3, Fig. 2D).

For number of false alarms, mean CFBmax scores did not exhibit a similar pattern as the other DAT parameters, with LEM having the lowest values (4.5–7.4), followed by SUV (7.5), PBO (9.2), and ZOL having the highest value (10.5) (Table 3). Only the mean CFBmax scores for ZOL were significantly different compared with PBO. All doses of LEM were significantly different than ZOL but not SUV (Fig. 2E).

For percentage of target hits, mean CFBmin values (corresponding with the highest level of observed impairment) showed a similar pattern across treatment groups as that observed for percentage over the road. All doses of LEM exhibited significantly higher CFBmin (smaller decrease in percentage of target hits) scores compared with ZOL (all P < 0.001) (Table 3). Lemborexant (20 mg) and LEM30 showed a significantly greater decrease in the percentage of target hits compared with SUV (P = 0.028 and P = 0.003, respectively); there was no significant difference between LEM10 and SUV. Mean CFBmin scores for LEM and the active comparators were significantly lower than for PBO (all P < 0.001) (Fig. 2F).

Safety

Lemborexant was generally well tolerated in Study 103, as was previously reported. Incidence of TEAEs during the main treatment phase was greater with all active comparators and all doses of LEM compared with PBO. As previously reported, the most common TEAE was somnolence, which was experienced by >85% of subjects after receiving each active treatment and was expected based on morning dosing, with no TEAE experienced by ≥12% of subjects. There were no deaths or serious AEs during the study, and no subjects were discontinued from the study because of adverse events. There were no trends of clinical concern based on analysis of mean values for laboratory parameters, vital signs, and electrocardiograms.

DISCUSSION

Results of the CRT and DAT assessments from Study 103 demonstrated that all active doses of LEM, ZOL, and SUV generally increased reaction time and reduced divided attention capabilities compared with PBO when administered in this daytime paradigm. Whereas all active treatments generally increased reaction time, indicating some cognitive impairment compared with PBO, results of the CRT suggest that all doses of LEM (10, 20, and 30 mg) were associated with less delay in reaction times compared with supratherapeutic (20 mg) dose of ZOL. Intermediate release
| Measure                        | Value                                                                 | Mean Value and Difference (Tested Drug Less Comparator) |
|-------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------|
|                               | PBO (n = 32) | ZOL (n = 32) | SUV (n = 32) | LEM10 (n = 32) | LEM20 (n = 32) | LEM30 (n = 32) |
| **Recognition RT, CFBmax*, ms** | Mean (SE)     | 82.4 (14.6)  | 164.2 (15.2) | 143.6 (18.4)  | 164.8 (22.4)  | 172.8 (18.9)  | 181.8 (23.3)  |
| Active–PBO                    | 89.4 (21.4)  | 62.8 (21.3)  | 76.3 (21.4)  | 90.4 (21.3)   | 102.2 (21.3)  | 107.4 (21.3)  |
| ZOL–LEM                       | 13.1 (21.7)  | −1.1 (21.4)  | −27.7 (21.3) | −12.8 (21.3)  | −39.4 (21.3)  | −56.2 (21.3)  |
| SUV–LEM                       | −13.5 (21.4) | −27.7 (21.3) | −39.4 (21.3) | −56.2 (21.3)  | −75.9 (21.3)  | −75.9 (21.3)  |
| Motor RT, CFBmax†, ms         | Mean (SE)     | 44.3 (6.7)   | 227.4 (17.8) | 83.0 (9.8)    | 86.6 (10.4)   | 102.9 (11.6)  | 97.9 (10.0)   |
| Active–PBO                    | 183.1 (19.3) | 26.0 (2.0, 62.0) | 42.2 (9.6)   | 58.6 (11.7)   | 74.2 (14.1)   | 89.4 (17.3)   |
| ZOL–LEM                       | 140.9 (18.2) | 124.5 (16.9) | 129.5 (19.6) | 145.6 (21.3)  | 160.6 (23.1)  | 175.7 (25.3)  |
| SUV–LEM                       | −3.5 (8.6)   | −19.9 (10.7) | −43.2 (17.6) | −57.4 (20.8)  | −70.5 (23.6)  | −83.8 (26.7)  |
| Total RT, CFBmax†, ms         | Mean (SE)     | 99.3 (16.9)  | 359.4 (24.9) | 197.7 (22.5)  | 229.5 (28.3)  | 246.7 (22.7)  | 258.7 (28.5)  |
| Active–PBO                    | 260.2 (29.8) | 98.5 (20.3)  | 130.3 (23.1) | 147.5 (26.5)  | 159.5 (30.3)  | 171.7 (32.1)  |
| ZOL–LEM                       | 129.9 (35.2) | 112.7 (31.0) | 132.9 (35.2) | 150.1 (37.5)  | 162.2 (40.1)  | 174.4 (42.3)  |
| SUV–LEM                       | −31.8 (26.3) | −49.0 (26.1) | −61.0 (29.9) | −72.1 (33.3)  | −83.2 (36.3)  | −94.4 (39.5)  |
| Percent correct, CFBmin%, %   | Mean (SE)     | −5.6 (2.42)  | −18.9 (1.59) | −5.5 (0.68)   | −8.8 (1.49)   | −9.1 (1.24)   | −10.9 (1.72)  |
| Active–PBO                    | −13.0 (−2.8 to −8.0) | −2.0 (−5.0 to 1.0) | −4.0 (−8.0 to 0.0) | −3.1 (−9.0 to 0.0) | −2.0 (−9.0 to 0.0) | −1.9 (−9.0 to 0.0) |
| ZOL–LEM                       | −10.1 (2.0)  | −9.8 (1.9)   | −7.9 (2.3)   | −6.0 (2.0)    | −4.0 (2.0)    | −2.0 (2.0)    |
| SUV–LEM                       | 2.0 (0.0–6.0) | 2.0 (−2.0 to 7.0) | 4.0 (1.0–8.0) | 2.0 (−2.0 to 7.0) | 4.0 (1.0–8.0) | 2.0 (−2.0 to 7.0) |

*For between-treatment differences, LSM (SE) difference is presented.
†For between-treatment differences, if a paired t test was used to assess the difference, mean (SE) difference is presented. If the sign test was used, median (first and third quartile) difference is presented.
‡Indicates statistically significant difference versus comparator.

CFBmax, maximum change from baseline; CFBmin, minimum change from baseline; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; LSM, least squares mean; PBO, placebo; RT, reaction time; SE, standard error; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.
and generally similar to supratherapeutic (40 mg) dose of SUV. This lesser delay for LEM and SUV suggests better ability to respond correctly, indicative of faster information processing and simple motor reaction abilities compared with ZOL, underscoring the mechanistic difference between x-drugs and DORAs.14

Divided attention capabilities measured by DAT were significantly worse for LEM, SUV, and ZOL than for PBO. However, values were significantly better with all doses of LEM compared with ZOL, indicating that undesired alterations of cognition may be more common with supratherapeutic doses of ZOL than LEM. Slower onset and lower magnitude of both cognitive function and psychomotor performance impairment was seen with LEM, as compared with ZOL, and these differences were paralleled by subjects' reports of feeling “stoned” and adverse effects related to intoxication and drunkenness, as have been previously reported. This has implications both for abuse potential assessment and safety, as slower onset and lower magnitude of effects related to intoxication may reduce negative effects such as loss of balance and falling.

The significant cognitive effects of LEM were observed within 8 hours postdose, which is the target pharmacologic period for the sleep-promoting effects of LEM and the time when most of the LEM is presumably metabolized.15 Significant cognitive effects for LEM were consistently absent at time points longer than 8 hours postdose even at supratherapeutic doses, contributing to other evidence for a low potential for residual/next-day effects after bedtime dosing. After the morning dosing used in this study, the majority of subjects were expected to experience somnolence, which may have affected the observations of impaired cognitive function.16 This suggests that the significant cognitive effects observed for LEM are likely secondary to the pharmacologic effect to promote sleep in the 8-hour period postdose. In a study examining the effects of LEM alone, alcohol alone, or alcohol and LEM coadministered, cognitive impairment (as measured by a battery of computerized assessments) was observed in subjects receiving morning dosing of LEM10 alone, peaking at 2 hours postadministration.17 In addition, in a study of the effects on automobile driving the morning after bedtime administration of LEM, no impairment was reported for subjects tested by a driving assessment 9 hours postadministration (the morning after) of LEM up to 10 mg.18 Previous studies have also reported no memory impairment with LEM versus PBO for therapeutic doses administered during the daytime.16 These findings together support that the expected somnolence with morning dosing of LEM had an effect on the cognitive and psychomotor performance of subjects in the current study. In addition, the dose response for LEM across the cognitive measures in this study was relatively flat, suggesting that there was no worsening of cognitive effects even at supratherapeutic doses and higher exposure.

Subjects who qualified for this study were healthy, nondependent, recreational sedative users who demonstrated the ability to distinguish both ZOL and SUV from PBO during screening. Therefore, these subjects differed from those in the DORA almoxe xant (ALM) and SUV abuse potential studies, as subjects in those studies were not screened for their ability to distinguish another DORA. The selection of subjects based on the ability to distinguish between active treatment and PBO may have resulted in increased sensitivity to discriminate between the drugs as compared with subjects from previously reported DORA abuse potential studies. Thus, the results of this trial may have a general relevance when considering abuse potential differences between drug classes.6,19

Lemborexant was generally well tolerated in this study, consistent with LEM phase 3 studies.1 The effect of LEM on cognitive function at supratherapeutic doses has been shown in this study to be generally favorable compared with the hypnotic ZOL and comparable with the DORA SUV. These observations are consistent with previous studies on the abuse potential of the
DORAs SUV and ALM.\textsuperscript{6,19} Suvorexant was shown to have significantly lesser effects on high VAS at therapeutic and supratherapeutic doses as compared with a supratherapeutic (30 mg) dose of ZOL,\textsuperscript{6} and ALM 400 mg (potential therapeutic dose) was shown to have significantly lower drug-liking VAS peak effect compared with 20 mg ZOL in previous reports.\textsuperscript{19} Both DORAs led to statistically higher drug-liking than PBO in those studies; however, comparison between SUV and ZOL was not an objective of Study 103.

Limitations of this study include the small sample sizes that are typically included in these studies, the resulting imbalance in the proportion of male and female subjects, and that nondependent recreational drug users represent only a subset of the drug abusing population.

**CONCLUSIONS**

Overall, these results suggest that, at the high therapeutic and supratherapeutic doses administered during the daytime, LEM led to significantly less impairment on cognitive performance than supratherapeutic doses of ZOL in this subject population of recreational sedative users. The lower impairment of LEM on cognitive function compared with ZOL and comparable effect compared

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**FIGURE 2.** Divided attention test over time. A, Root mean square distance and mean DAT over time, (B) greatest distance from center of the road, (C) percent time over road, (D) response latency: correct response, (E) number of false alarms, and (F) percentage of target hits. SUV indicates suvorexant 40 mg; ZOL, zolpidem 30 mg, DAT, divided attention test; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; PBO, placebo; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.
### TABLE 3. Findings for Cognitive Outcome Measure: Divided Attention Task

| Measure                                      | Value                  | PBO (n = 32) | ZOL (n = 32) | SUV (n = 32) | LEM10 (n = 32) | LEM20 (n = 32) | LEM30 (n = 32) |
|----------------------------------------------|------------------------|--------------|--------------|--------------|----------------|----------------|----------------|
| **Percentage of target hits, CFB<sub>min</sub>*** | Mean (SE)              | −17.8 (3.1)  | −62.1 (3.7)  | −36.7 (3.3)  | −43.3 (3.6)    | −43.8 (3.7)    | −45.6 (3.5)    |
| Lower percentage = greater impairment        | Active–PBO             | −44.1 (3.6)  | −17.1 (3.6)  | −21.2 (3.6)  | −25.0 (3.6)    | −28.0 (3.6)    | −16.1 (3.6)    |
|                                               | ZOL–LEM                | −22.9 (3.6)  | −9.1 (3.6)   | −19.1 (3.6)  | −16.1 (3.6)    | −16.1 (3.6)    | −16.1 (3.6)    |
|                                               | SUV–LEM                | −4.1 (3.6)   | −7.9 (3.6)   | −7.9 (3.6)   | −10.9 (3.6)    | −10.9 (3.6)    | −10.9 (3.6)    |
| **Percentage of time over road, CFB<sub>min</sub>*** | Mean (SE)              | −12.7 (2.4)  | −45.3 (2.4)  | −29.9 (2.2)  | −34.1 (3.1)    | −33.9 (2.9)    | −35.0 (3.0)    |
| Lower percentage = greater impairment         | Active–PBO             | −33.7 (2.4)  | −15.1 (2.4)  | −19.0 (2.4)  | −22.0 (2.4)    | −22.8 (2.4)    | −22.8 (2.4)    |
|                                               | ZOL–LEM                | −14.7 (2.4)  | −11.7 (2.4)  | −10.9 (2.4)  | −10.9 (2.4)    | −10.9 (2.4)    | −10.9 (2.4)    |
|                                               | SUV–LEM                | −3.9 (2.4)   | −6.9 (2.4)   | −7.6 (2.4)   | −7.6 (2.4)     | −7.6 (2.4)     | −7.6 (2.4)     |
| **RMS distance, CFB<sub>max</sub>*, pixels**  | Mean (SE)              | 19.3 (4.1)   | 68.0 (4.2)   | 48.1 (5.0)   | 56.8 (5.9)     | 57.6 (5.8)     | 59.9 (6.3)     |
| Longer distance = greater impairment          | Active–PBO             | 2.5 (0.5–5.5) | 0.0 (−2.5–2.5) | 1.0 (−2.0 to 2.0) | 2.0 (0.0–8.0) | 1.5 (−1.0 to 7.5) | 1.5 (−1.0 to 7.5) | 1.5 (−1.0 to 7.5) |
|                                               | ZOL–LEM                | 34.6 (4.8)   | 13.8 (4.7)   | 10.6 (4.7)   | 9.9 (4.8)      | 9.9 (4.8)      | 9.9 (4.8)      |
|                                               | SUV–LEM                | 8.0 (4.7)    | −13.2 (4.8)  | −13.2 (4.8)  | −13.2 (4.8)    | −13.2 (4.8)    | −13.2 (4.8)    |
| **Mean greatest distance, CFB<sub>max</sub>*, pixels** | Mean (SE)              | 73.2 (10.9)  | 171.5 (11.1) | 139.9 (11.1) | 155.3 (11.9)   | 151.0 (11.4)   | 157.0 (10.7)   |
| Longer distance = greater impairment          | Active–PBO             | 96.5 (10.3)  | 56.3 (10.4)  | 74.4 (10.3)  | 79.0 (10.3)    | 82.7 (10.3)    | 82.7 (10.3)    |
|                                               | ZOL–LEM                | 22.1 (10.3)  | 17.5 (10.3)  | 17.5 (10.3)  | 13.8 (10.3)    | 13.8 (10.3)    | 13.8 (10.3)    |
|                                               | SUV–LEM                | −8.1 (10.3)  | −22.7 (10.4) | −26.3 (10.4) | −26.3 (10.4)   | −26.3 (10.4)   | −26.3 (10.4)   |
| **Response latency of correct response, CFB<sub>max</sub>*, ms** | Mean (SE)              | 66.4 (8.1)   | 154.8 (15.2) | 128.3 (11.1) | 130.1 (12.2)   | 129.3 (13.8)   | 146.5 (13.9)   |
| Longer times = greater impairment             | Active–PBO             | 88.4 (53.1–123.7) | 61.9 (36.7–87.1) | 63.7 (34.8–92.7) | 62.9 (31.3–94.5) | 80.1 (47.1–113.0) | 80.1 (47.1–113.0) |
|                                               | ZOL–LEM                | 24.7 (−13.9 to 63.3) | 25.5 (−5.1 to 56.1) | 8.3 (−30.5 to 47.1) | 8.3 (−30.5 to 47.1) | 8.3 (−30.5 to 47.1) | 8.3 (−30.5 to 47.1) |
|                                               | SUV–LEM                | 4.0 (−20.0 to 33.0) | −1.0 (−34.0 to 32.0) | −18.2 (−46.0 to 9.5) | −18.2 (−46.0 to 9.5) | −18.2 (−46.0 to 9.5) | −18.2 (−46.0 to 9.5) |

*For between-treatment differences, LSM (SE) difference is presented.
1 For between-treatment differences, if a paired t test was used to assess the difference, mean (SE) difference is presented. If the sign test was used, median (first and third quartile) difference is presented.
2 Indicates statistically significant difference versus comparator.

LSM indicates least squares mean; PBO, placebo; SE, standard error; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.
with SUV is consistent with the assessment of LEM abuse potential relative to ZOL and SUV in Study 103. The cognitive effects of LEM were mostly observed in the therapeutic target period of up to 8 hours postdose, suggesting that the observed cognitive effects may be due to the expected sleep-promoting effect of LEM.

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AUTHOR DISCLOSURE INFORMATION

M.M., N.H., J.A., G.F., L.R., and I.L. 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, and J.H. is an employee of Pinney Associates.

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

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