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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 (CFB_{max}) 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 CFB_{max} 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 CFB_{max} 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

(*J Clin Psychopharmacol* 2022;42: 374–382)

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-G00-303 (Study 303; SUNRISE-2; NCT02952820).[1,2] 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.[3] In contrast, benzodiazepine hypnotics 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[4]) 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.[4,5] 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.[6]

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.

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Received January 6, 2022; accepted after revision April 9, 2022.

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ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000001562

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.

During the qualification phase, subjects received a single oral dose of ZOL 30 mg, SUV 40 mg, or PBO in a randomized, double-dummy, double-blind, 3-period crossover manner under fasted conditions. A ≥15-point peak (E_{max}) increase on the bipolar "at this moment" drug-liking visual analog scale (VAS) in response to ZOL and SUV relative to PBO was used to confirm that subjects could distinguish ZOL 30 mg and SUV 40 mg from PBO after drug administration. Eligible subjects rated ZOL and SUV with a peak VAS score of ≥65 and PBO a peak VAS score of ≥40 and ≤60. Subjects were also required to demonstrate consistent responses on other subjective measures and ability to tolerate the treatments as well as demonstrate general behavior suggestive that the subject could successfully complete the study.

During the main treatment phase, study drug (PBO, ZOL, SUV, LEM10, LEM20, and LEM30) was administered in a triple-dummy fashion, and each treatment period was separated by a washout interval of at least 14 days. An approximate 14-day follow-up period occurred immediately after the final study drug administration and concluded with an end of study visit.

Cognitive Performance Assessments

Objective cognitive performance of study subjects was assessed using the CRT task and the DAT, predose (baseline) and at prespecified time points from 0.25 to 24 hours after study drug administration as used in similar abuse studies.[8–11] Choice reaction test is a metric of psychomotor performance and comprises the following measures: recognition reaction time (RRT), motor reaction time (MRT), and total reaction time (TRT). Recognition reaction time is defined as the time it takes for a subject to react to the illumination of a signal light by lifting their finger from a button, with higher scores (longer reaction times) indicating greater impairment. Motor reaction time is defined as the time between subject lifting their finger from the button and pressing a response button, with higher scores (longer reaction times) indicating greater impairment. Total reaction time is the sum of RRT and MRT, with higher scores indicating greater impairment. Maximum change from baseline (CFB_{max}) was assessed for MRT, RRT, and TRT. The minimum change from baseline (CFB_{min}) for the percentage of correct responses was also assessed.

During the CRT test, the subject is presented with an onscreen equivalent of the numeric keypad. The subject is asked to quickly press the buttons on a separate keypad that correspond to the keys illuminated on the screen. For a given trial, 4 to 8 numbered squares that correspond spatially to the response keys on the keypad are illuminated on the computer screen. The sequence of key illumination is random and follows a pattern that alternates between the center button and any button that was part of the stimuli set of buttons. The stimulus set size progresses from 4 to 6 to 8 during the test. The number of alternative choices increases over blocks of responses in each cycle.[12]

Divided attention test is a manual-tracking test with a simultaneous visual target detection component. During testing, the subject is presented with the image of an airplane, controlled by the subject with a joystick, and a randomly curving road. As the road moves down the screen, the subject is tasked to position the image of the airplane over the center of the road and to press a button on the joystick in response to randomly appearing targets.[13]

Divided attention test assessments included the percentage of target hits, with lower scores indicating greater impairment; the percentage of time over the road, with lower percentages indicating greater impairment; and the number of false alarms with the subject pressing the button when no target has appeared, with higher scores indicating greater impairment. Root mean square (RMS) distance from the center of the road (pixels) was assessed, with longer distances indicating greater impairment. Also assessed was greatest distance from the center of the road (pixels), with longer distances indicating greater impairment. Response latency of correct responses (milliseconds) was assessed, with longer response latencies indicating greater impairment. Minimum change from baseline was assessed for the percentage of time over the road and percentage of target hits, and CFB_{max} was assessed for RMS distance from center of the road, mean greatest distance from the center of the road, mean response latency of correct responses, and the number of false alarms.

Statistical Analyses

Cognition endpoints were analyzed in the completer 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* CFB_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
Motor RT* CFB_{max}	>	>	>	>	>	>	>	>	NS	NS	NS
Total RT* CFB_{max}	>	>	>	>	>	>	>	>	NS	NS	<
Percentage correct† CFB_{min}	<	<	<	<	<	<	<	<	>	>	>
Divided attention task											
RMS distance from center of road* CFB_{max}	>	>	>	>	>	>	>	>	NS	<	<
Greatest distance from center of road* CFB_{max}	>	>	>	>	>	>	NS	NS	NS	<	<
Response latency of correct responses* CFB_{max}	>	>	>	>	>	NS	NS	NS	NS	NS	NS
No. false alarms* CFB_{max}	>	NS	NS	NS	NS	>	>	>	NS	NS	NS
Percentage of time over road‡ CFB_{min}	<	<	<	<	<	<	<	<	NS	>	>
Percentage of target hits‡ CFB_{min}	<	<	<	<	<	<	<	<	NS	>	>

> 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_{min} 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 CFB_{max} 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 CFB_{max} 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 CFB_{max} (larger mean increase in MRT) scores compared with all doses of LEM (all $P < 0.001$), but mean CFB_{max} scores for LEM and SUV were not significantly different (Table 2).

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

For the percentage of correct responses, mean CFB_{min} 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 CFB_{min} (smaller decrease in percentage correct) compared with ZOL (all $P \leq 0.001$). All doses of LEM exhibited significantly lower mean CFB_{min} (greater decrease in percentage correct) compared with SUV (all $P < 0.05$). For LEM, SUV, and ZOL, CFB_{max} for RRT, MRT, 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 CFB_{max} 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 CFB_{max} scores compared with SUV ($P = 0.007$ and $P = 0.004$, respectively), indicative of reduced motor precision (Table 3). Mean CFB_{max} scores for LEM, ZOL, and SUV were significantly higher compared with PBO. 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 CFM_{max} values followed a similar pattern across treatment groups as that observed for RMS distance. Lemborexant (10 mg) showed significantly lower mean CFB_{max} compared with ZOL (Table 3). Lemborexant (20 mg) and LEM30 showed significantly higher mean CFB_{max} compared with SUV. Mean CFB_{max} scores for LEM and the active comparators were significantly higher compared with PBO (Fig. 2B).

All doses of LEM exhibited statistically significant higher CFB_{min} 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 CFB_{min} scores compared with SUV. Mean CFB_{min} 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 CFB_{max} values followed a similar pattern seen for RMS distance. Mean CFB_{max} 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 CFB_{max} 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 CFB_{max} 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 CFB_{min} 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 CFB_{min} (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 CFB_{min} 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.[7] 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

TABLE 2. Findings for Cognitive Outcome Measure: Choice Reaction Time

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, CFB_{max}*, 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)
Longer times = greater impairment	Active–PBO		89.4 (21.4)‡	62.8 (21.3)‡	76.3 (21.4)‡	90.4 (21.3)‡	102.2 (21.3)‡
	ZOL–LEM				13.1 (21.7)	−1.1 (21.4)	−12.8 (21.3)
	SUV–LEM				−13.5 (21.4)	−27.7 (21.3)	−39.4 (21.3)
Motor RT, $CFB^{\dagger}_{max}$, 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)
Longer times = greater impairment	Active–PBO		183.1 (19.3)‡	26.0 (2.0, 62.0)‡	42.2 (9.6)‡	58.6 (11.7)‡	53.6 (11.4)‡
	ZOL–LEM				140.9 (18.2)‡	124.5 (16.9)‡	129.5 (19.6)‡
	SUV–LEM				−3.5 (8.6)	−19.9 (10.7)	−14.9 (7.7)
Total RT, $CFB^{\dagger}_{max}$, 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)
Longer times = greater impairment	Active–PBO		260.2 (29.8)‡	98.5 (20.3)‡	130.3 (23.1)‡	147.5 (26.5)‡	159.5 (30.3)‡
	ZOL–LEM				129.9 (35.2)‡	112.7 (31.0)‡	90.5 (17.0, 210.0)‡
	SUV–LEM				−31.8 (26.3)	−49.0 (26.1)	−61.0 (25.9)‡
Percent correct, CFB_{min}, %	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)
More negative = greater impairment	Active–PBO		−13.0 (−22.0 to −8.0)‡	−2.0 (−5.0 to 1.0)‡	−4.0 (−8.0 to 0.0)‡	−3.0 (−9.0 to 0.0)‡	−5.0 (−10.0 to 0.0)‡
	ZOL–LEM				−10.1 (2.0)‡	−9.8 (1.9)‡	−7.9 (2.3)‡
	SUV–LEM				2.0 (0.0–6.0)‡	2.0 (−2.0 to 7.0)‡	4.0 (1.0–8.0)‡

*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.

CFB_{max}, maximum change from baseline; CFB_{min}, 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.

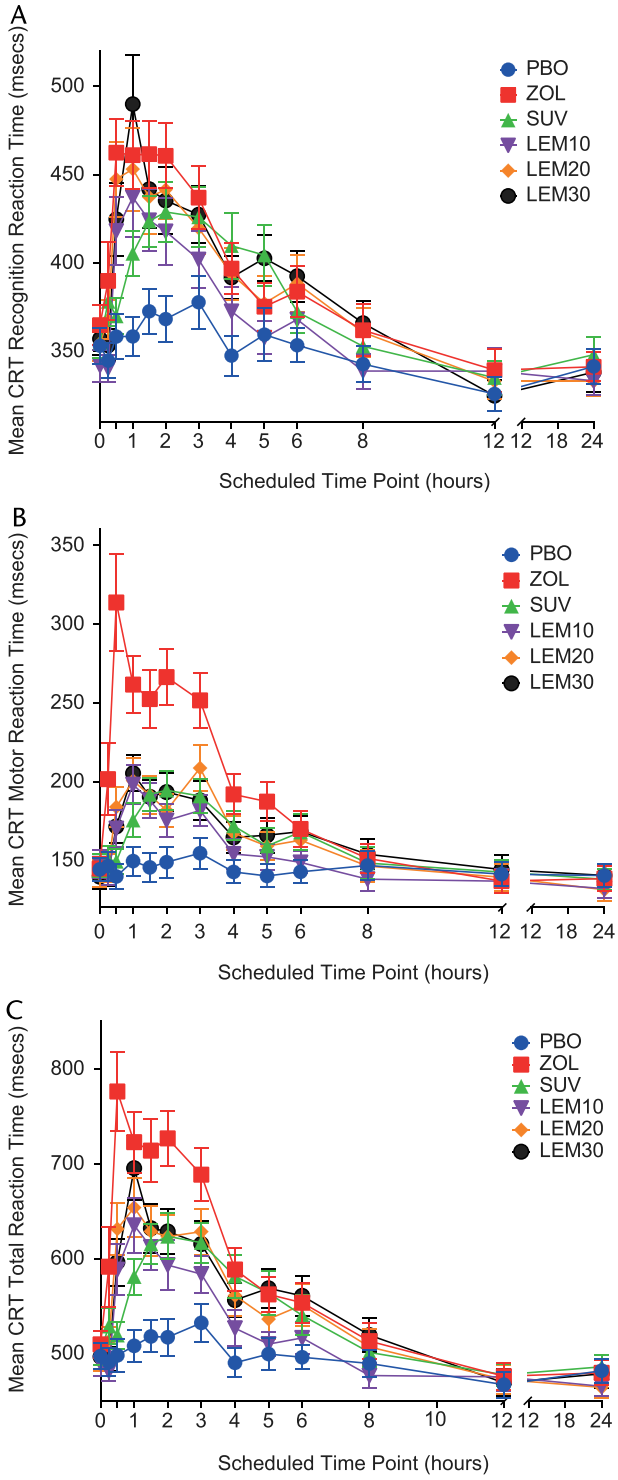

FIGURE 1. Mean CRT over time. A, Recognition reaction time, (B) MRT, and (C) total response time. SUV indicates suvorexant 40 mg; ZOL, zolpidem 30 mg; CRT, Choice Reaction Time; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; PBO, placebo; SUV, suvorexant 40 mg; ZOL, zolpidem 30 mg.

and generally similar to supratherapeutic (40 mg) dose of SUV. This lesser delay for LEM and SUV subjects suggests better ability to respond correctly, indicative of faster information processing and simple motor reaction abilities compared with ZOL, underscoring the mechanistic difference between z-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 almorexant (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

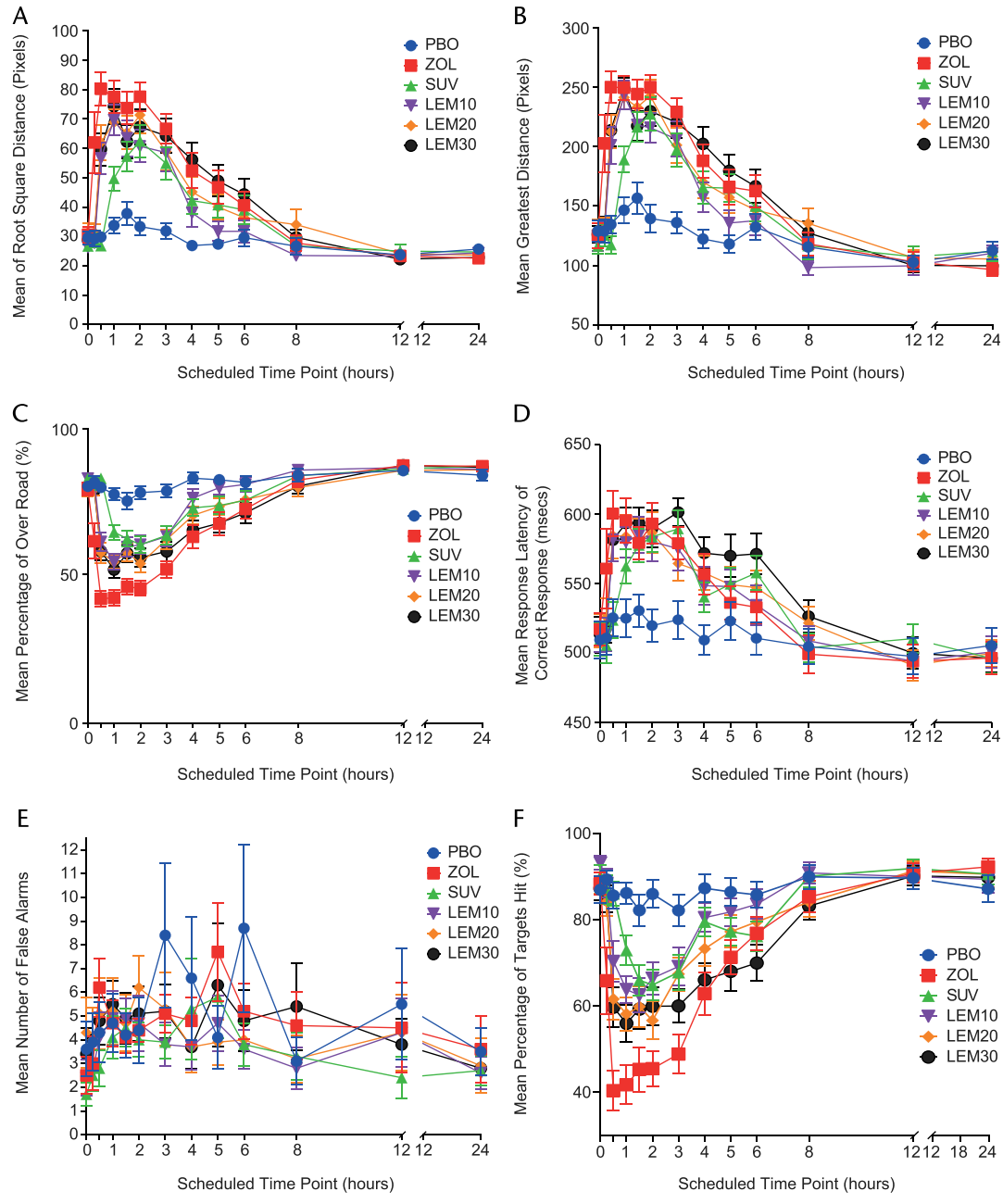

FIGURE 2. Divided attention test over time. A, Root mean square distance and mean DAT over time, (B) greatest distance from center of the road, (C) percent time over road, (D) response latency: correct response, (E) number of false alarms, and (F) percentage of target hits. SUV indicates suvorexant 40 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.

DORAs SUV and ALM.[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,[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.[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

TABLE 3. Findings for Cognitive Outcome Measure: Divided Attention Task

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)
Percentage of target hits, CFB_{min}*	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)‡
	ZOL–LEM				−22.9 (3.6)‡	−19.1 (3.6)‡	−16.1 (3.6)‡
	SUV–LEM				4.1 (3.6)	7.9 (3.6)‡	10.9 (3.6)‡
Percentage of time over road, CFB_{min}*	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)
	ZOL–LEM				−14.7 (2.4)	−11.7 (2.4)	−10.9 (2.4)
	SUV–LEM				3.9 (2.4)	6.9 (2.4)	7.6 (2.4)
No. false alarms, $CFB^{\dagger}_{max}$	Mean (SE)	9.2 (3.4)	10.5 (2.0)	7.5 (1.8)	5.8 (1.0)	4.5 (0.8)	7.4 (2.4)
Higher scores = greater impairment	Active–PBO		2.5 (0.5–5.5)‡	0.0 (−2.5– to 2.5)	1.0 (−2.0 to 2.0)	0.0 (−3.0 to 1.5)	1.5 (−3.5 to 4.0)
	ZOL–LEM				3.0 (0.0–5.5)‡	2.0 (0.0–8.0)‡	1.5 (−1.0 to 7.5)‡
	SUV–LEM				0.0 (−2.0 to 2.0)	1.0 (−1.0 to 4.0)	0.1 (2.0)
RMS distance, CFB_{max}*, 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		50.5 (4.7)‡	26.7 (4.8)‡	34.6 (4.8)‡	39.9 (4.7)‡	40.6 (4.7)‡
	ZOL–LEM				15.8 (4.8)‡	10.6 (4.7)‡	9.9 (4.8)‡
	SUV–LEM				−8.0 (4.7)	−13.2 (4.8)‡	−13.9 (4.8)‡
Mean greatest distance, CFB_{max}*, 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)‡
	ZOL–LEM				22.1 (10.3)‡	17.5 (10.3)	13.8 (10.3)
	SUV–LEM				−18.1 (10.3)	−22.7 (10.4)‡	−26.3 (10.4)‡
Response latency of correct response, $CFB^{\dagger}_{max}$, 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)‡
	ZOL–LEM				24.7 (−13.9 to 63.3)	25.5 (−5.1 to 56.1)	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)

*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.

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.

ACKNOWLEDGMENTS

This study was supported by Eisai Inc. The investigators retained full independence in the conduct of this research. Medical writing assistance was provided by Charles Cheng, MS, of Envision Pharma Group, and was funded by Eisai Inc. The services of Envision complied with international guidelines for Good Publication Practice (GPP3).

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.

REFERENCES

1. Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep*. 2020;43.
2. Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. *JAMA Netw Open*. 2019;2:e1918254.
3. Beuckmann CT, Suzuki M, Ueno T, et al. In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin receptor antagonist. *J Pharmacol Exp Ther*. 2017;362:287–295.
4. Food and Drug Administration. Assessment of Abuse Potential of Drugs: Guidance for Industry. Available at: https://www.fda.gov/media/116739/download. Accessed September 24, 2020.
5. Gould TJ. Addiction and cognition. *Addict Sci Clin Pract*. 2010;5:4–14.
6. Schoedel KA, Sun H, Sellers EM, et al. Assessment of the abuse potential of the orexin receptor antagonist, suvorexant, compared with zolpidem in a randomized crossover study. *J Clin Psychopharmacol*. 2016;36:314–323.
7. Landry I, Hall H, Aluri J, Filippov G, Reyderman L, Setnik B, Henningfield J, Moline M. Abuse potential of lemborexant, a dual orexin receptor antagonist, compared with zolpidem and suvorexant in recreational sedative users. *J Clin Psychopharmacol*. 2022;42:363–373.
8. Ferrara SD, Giorgetti R, Zancaner S, et al. Effects of single dose of gamma-hydroxybutyric acid and lorazepam on psychomotor performance and subjective feelings in healthy volunteers. *Eur J Clin Pharmacol*. 1999;54:821–827.
9. Gustavsen I, Hjelmeland K, Bernard JP, et al. Individual psychomotor impairment in relation to zopiclone and ethanol concentrations in blood—a randomized controlled double-blinded trial. Addiction 2012;107:925–932.
10. Jones JD, Bisaga A, Metz VE, et al. The PPARgamma agonist pioglitazone fails to alter the abuse potential of heroin, but does reduce heroin craving and anxiety. *J Psychoactive Drugs*. 2018;50:390–401.
11. Levy-Cooperman N, Schoedel KA, Chakraborty B, et al. Abuse liability assessment of eslicarbazepine acetate in healthy male and female recreational sedative users: a phase I randomized controlled trial. *Epilepsy Behav*. 2016;61:63–71.
12. Hindmarch I, Rigney U, Stanley N, et al. Pharmacodynamics of milnacipran in young and elderly volunteers. *Br J Clin Pharmacol*. 2000;49:118–125.
13. Kaplan HL. Representation of on-line questionnaires in an editable, auditable database. *Behav Res Methods Instrum Comput*. 1992;24:373–384.
14. Atkin T, Comai S, Gobbi G. Drugs for insomnia beyond benzodiazepines: pharmacology, clinical applications, and discovery. *Pharmacol Rev*. 2018;70:197–245.
15. Ueno T, Ishida T, Aluri J, et al. Disposition and metabolism of [(14)C] lemborexant in healthy human subjects and characterization of its circulating metabolites. *Drug Metab Dispos*. 2021;49:31–38.
16. Moline M, Zammit G, Yardley J, et al. Lack of residual morning effects of lemborexant treatment for insomnia: summary of findings across 9 clinical trials. *Postgrad Med*. 2021;133:71–81.
17. Landry I, Hall N, Aluri J, et al. Effect of alcohol coadministration on the pharmacodynamics, pharmacokinetics, and safety of lemborexant. American College of Neuropsychopharmacology Congress; December 8–11, 2019; Orlando, FL.
18. Vermeeren A, Jongen S, Murphy P, et al. On-the-road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers. *Sleep*. 2019;42.
19. Cruz HG, Hoever P, Chakraborty B, et al. Assessment of the abuse liability of a dual orexin receptor antagonist: a crossover study of almorexant and zolpidem in recreational drug users. *CNS Drugs*. 2014;28:361–372.