Original Paper

Effect of alcohol coadministration on the pharmacodynamics, pharmacokinetics, and safety of lemborexant: A randomized, placebo-controlled crossover study

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Abstract

Background: Lemborexant is a dual orexin receptor antagonist approved to treat insomnia in adults in several countries including the USA, Canada, and Japan.

Aims: This study was conducted to investigate effects of lemborexant and alcohol coadministration on postural stability, cognitive performance, and the pharmacokinetics, safety, and tolerability of lemborexant.

Methods: This was a Phase 1, double-blind, placebo-controlled, four-period crossover study in 32 healthy adults. Individuals were randomized into one of four treatment sequences to receive single doses of placebo, lemborexant 10 mg (LEM10), alcohol (males, 0.7 g/kg; females, 0.6 g/kg), and LEM10 plus alcohol, each separated by a 14-day washout. Postural stability (body sway) was measured by ataxiameter and a cognitive performance assessment battery evaluated four domains of attention and memory.

Results: Pharmacodynamic outcomes were analyzed for the 18 participants who completed all four treatments. Change from baseline in body sway showed no significant differences between lemborexant plus alcohol versus alcohol alone. Compared with alcohol alone, coadministration of lemborexant with alcohol showed additive negative effects on cognitive performance domains, corresponding approximately with peak plasma lemborexant concentrations (median = 1.5 h). Cognitive performance was also impaired with lemborexant alone at 0.5 and 2 h in this experimental paradigm with morning dosing. Alcohol increased plasma lemborexant exposure by 70% based on area under the curve to 72 h, and increased peak plasma lemborexant concentrations by 35%. The most commonly reported treatment–emergent adverse event was somnolence.

Conclusion: Coadministration of lemborexant with alcohol showed additive negative effects on cognitive measures, but not on postural stability, compared with alcohol alone. Lemborexant exposure was increased with alcohol. Lemborexant alone or with alcohol was well tolerated. Patients are advised not to consume alcohol with lemborexant.

Keywords
Lemborexant, alcohol, insomnia, drug–drug interaction

Introduction

Insomnia is a common sleep–wake disorder, with 30–50% of the adult population experiencing occasional short-term symptoms, and up to 10% meeting diagnostic criteria for insomnia disorder (Chung et al., 2015; Sateia et al., 2017; Uhlig et al., 2014). The societal burden of insomnia is substantial, with well-established relationships between poor sleep quality and impaired daytime functioning (Kayaba et al., 2020), underperformance in the workplace (Kessler et al., 2011), substance abuse (Lee et al., 2019), psychiatric and medical comorbidities (Blanken et al., 2020; Meaklim et al., 2018; Walsh et al., 2011; Wickwire et al., 2019), and increased healthcare resource utilization (Wickwire et al., 2019). Common strategies for the treatment of sleep onset and/or sleep maintenance insomnia include cognitive behavioral therapy for insomnia or pharmacotherapy with benzodiazepines, nonbenzodiazepine Z-drugs, and antidepressants with sedative properties (Sateia et al., 2017). However, these pharmacotherapies may be associated with adverse sleep-related behaviors and cognitive/psychomotor impairment, affecting driving performance and increasing the risk of falls in elderly patients (Asnis et al., 2015; Riemann et al., 2017).

Insomnia treatments may be taken regularly for extended periods, increasing the possibility that individuals will take their medication after having consumed alcohol. As the result of the sedative effects of alcohol, individuals may also use alcohol to

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self-treat insomnia (Vitiello, 1997). Alcohol consumption is known to impair sustained attention, disrupt the ability to learn new information, impair coordination, increase body sway, and to lower self-rated alertness (van Harten et al., 1992; Wesnes et al., 2000). In addition, alcohol consumption is associated with falls, accidents, and accident-related injuries (Chen and Yoon, 2017; Kurzthaler et al., 2005; Taylor et al., 2010). Therefore, it is considered of clinical importance to assess the combination of alcohol with new sleep-promoting drugs to determine the potential consequence of the combination.

Lemborexant is an orally active, dual orexin receptor antagonist (DORA) approved in multiple countries, including the USA, Japan, Canada, Australia, and several Asian countries for the treatment of insomnia in adults. In randomized controlled trials of adults with insomnia disorder, lemborexant 5 and 10 mg improved sleep onset and sleep maintenance compared with placebo without producing clinically meaningful residual morning sleepiness (Kärppä et al., 2020; Murphy et al., 2017, 2020; Rosenberg et al., 2019). During the clinical development of lemborexant, the potential for residual effects with single and chronic dosing was assessed in nine clinical studies using a variety of measures, including postural stability, cognitive performance, and on-road driving. A recently published overview of these studies indicated that lemborexant has a low propensity to impair next-day functioning among healthy subjects and subjects with insomnia (Moline et al., 2021).

Additive negative effects on psychomotor performance have been shown with other DORAs when coadministered with alcohol. Almorexant plus alcohol led to additive negative effects on saccadic peak velocity, adaptive tracking performance, and subjective alertness (Hoch et al., 2013). Suvorexant coadministered with alcohol increased reaction time versus either component alone and had additive negative effects on tests of vigilance, working/episodic memory, postural stability and alertness (Sun et al., 2015). Suvorexant, lemborexant, and recently, daridorexant (Berger et al., 2020), are the only DORAs currently approved for insomnia; almorexant is no longer in clinical development. Interactions with alcohol have also been demonstrated for other sleep agents, including zopiclone and triazolam (Kuitunen et al., 1990). No pharmacokinetic interactions were observed between alcohol and either almorexant, suvorexant, or other sleep agents to explain these additive negative effects (Hoch et al., 2013; Kuitunen et al., 1990; Sun et al., 2015).

Evaluation of the effects of concomitant lemborexant and alcohol administration in humans was included in the clinical development program for global registrations. This study assessed the effects on postural stability and cognitive performance of single morning doses of alcohol and lemborexant each administered alone and in combination to healthy adults. The effects of concomitant alcohol administration on the pharmacokinetic properties and the safety and tolerability of lemborexant were also assessed.

Methods

Study design

This was a Phase 1, single-center, randomized, double-blind, placebo-controlled, single-dose, four-period crossover study (NCT03483636; E2006-A001-009) that examined the potential for a drug–drug interaction between lemborexant and alcohol in healthy individuals. The protocol and protocol amendments were approved by the Investigational Review Board for the study site (INC Research Toronto, Toronto, ON, Canada) and the study was conducted in accordance with the Good Clinical Practice guidelines as required by the principles of the Declaration of Helsinki and other applicable local and national regulations. All participants provided written informed consent before entering the study.

Participants

Eligible participants were healthy males or females, 19–55 years of age, with a body mass index of 22–33 kg/m^2 and a minimum weight of 55 kg. Individuals were occasional or regular drinkers, defined as consuming at least two standard alcoholic drinks per week but not more than two per day in an average week (equaling two to 14 standard drinks per week) during the 6 months before screening. Major exclusion criteria were moderate or severe alcohol use disorder within the past 2 years, or the presence of insomnia, narcolepsy, obstructive sleep apnea, or restless legs syndrome. Subjects were not to take prescription or over-the-counter medications within 2 weeks prior to dosing and throughout the study, including washout periods.

Procedures

Following a screening period of up to 30 days, eligible participants entered the randomization phase comprised of four 72-h treatment periods, each separated by a 14-day washout period, and a final end-of-study/early withdrawal visit. Participants were randomly assigned to one of four treatment sequences and received a single dose of each of the following four treatments during the study (one treatment during each period): placebo (lemborexant placebo plus alcohol placebo); lemborexant 10 mg alone (plus alcohol placebo); alcohol alone (40% ethanol (v/v) vodka diluted in a low-calorie beverage plus lemborexant placebo); and lemborexant 10 mg plus alcohol. The randomized treatment sequences were based on a Williams design 4 × 4 Latin square, as is standard for a four-way crossover study. The dose of alcohol was 0.7 g/kg for males and 0.6 g/kg for females, equivalent to approximately three standard drinks (0.7 g/kg × 60 kg; a standard drink contains approximately 14 g of alcohol). A lower dose of alcohol was administered to females because they tend to reach higher peak blood alcohol concentrations than males, even after adjusting for differences in body weight (Mumenthaler et al., 1999). The alcohol placebo consisted of 1 mL of alcohol floated on top of a nonalcoholic drink to mimic the smell and taste of alcohol. Participants were to abstain from alcohol for 48 h before the start of each treatment period and to have a negative alcohol breath test before each admission to the clinic. Doses were administered approximately 2 h after wake time following a light breakfast (between approximately 9:00 and 11:00), and participants were assessed for 72 h in the clinic after each dose. The light breakfast was added as a protocol amendment to improve tolerability. The randomization code was generated by the designated unblinded statistician before the start of the study and assigned by the investigator using sealed envelopes. Participants and clinic staff were blinded to treatment assignment except for unblinded pharmacists.

Assessments

Study assessments included postural stability (body sway), cognitive performance, lemborexant pharmacokinetics, and safety. The coprimary endpoints were change from baseline in body sway and power of attention (from the cognitive performance test) for lemborexant plus alcohol versus lemborexant or alcohol alone, and the safety and tolerability of lemborexant alone and in combination with alcohol. These types of psychomotor and cognitive assessments have been used in prior studies to examine drug interactions with alcohol (Hoch et al., 2013; Sun et al., 2015; Wesnes et al., 2000). In particular, the power of attention test has been shown to be sensitive to the impairing effects of alcohol (Sun et al., 2015; Wesnes, 2000).

Postural stability. Postural stability was assessed using an ataxiameter that measures body sway via a cable around the individual's waist. Body sway is measured in units of one-third degree angle of arc, with higher values indicating more body sway and less postural stability (Wright, 1971). Participants were instructed to stand with their feet shoulder-width apart and eyes closed while body sway was measured for 60 s. Postural stability assessments were conducted predose and at 0.5, 2, 6, 9, 12, 24, 48, and 72 h postdose in each treatment period. Participants received familiarization training before the start of data collection, and each individual was to adopt consistent foot positioning for all of their postural stability assessments.

Cognitive performance. The cognitive performance assessment battery (CPAB) was administered after each postural stability test (Wesnes, 2000). The computerized CPAB consisted of nine tasks assessing memory and attention (simple reaction time, choice reaction time, digit vigilance, immediate word recall, delayed word recall, numerical working memory, spatial working memory, word recognition, and picture recognition), and was the same battery employed in one of the Phase 3 pivotal studies (Moline et al., 2021). Four composite domain scores were calculated for power of attention, continuity of attention, quality of memory, and speed of memory retrieval. The power of attention domain was calculated from the speed scores of the simple reaction time, choice reaction time, and digit vigilance tasks, with lower scores indicating better performance. The continuity of attention domain measures the ability to sustain attention and was calculated by combining the accuracy scores from the simple reaction time, choice reaction time, and digit vigilance tests, with higher scores indicating better performance. The quality of memory domain score measures the ability to store and retrieve information and combined the accuracy measures from the tests of working memory (numerical and spatial) and episodic memory (immediate word recall, delayed word recall, word recognition, and picture recognition), with higher scores indicating better performance. The speed of memory retrieval domain combined the reaction time scores from the working memory (numerical and spatial) and episodic recognition tests (word recognition and picture recognition), with lower scores indicating better performance. Participants received training in the CPAB tasks the day prior to study drug administration in each treatment period, including completing all nine CPAB tasks at least twice before the first treatment period and at least once before each of the remaining treatment periods.

Pharmacokinetics. Blood samples were collected immediately predose and at predetermined intervals up to 72 h after dosing for assessment of plasma concentrations of lemborexant and the major metabolites M4, M9, and M10 (Ueno et al., 2021) using a validated liquid chromatography coupled with the tandem mass spectrometry method that has been described previously (Landry et al., 2021b). The inter-day and intra-day precision and accuracy were less than 15% across lemborexant and its metabolites. Blood ethanol concentrations were measured from samples taken predose and at 0.5 and 2 h after dosing and using a validated gas chromatography with mass spectrometry method following protein precipitation with 1-propanol as the internal standard. Accuracy and precision were less than ±14% in whole blood and less than ±7% in plasma. Noncompartmental pharmacokinetic parameters calculated for lemborexant and its metabolites included maximum observed plasma concentration (C_{max}), time to reach C_{max} after dosing (t_{max}), and area under the concentration–time curve from time 0 to 72 h (AUC_{0-72}).

Safety. Safety was assessed based on adverse events (AEs), blood chemistry, hematology, and urinalysis, vital signs, physical examinations (including neurological assessments), and electrocardiograms. The AEs were graded for severity and relationship to study treatments.

Statistical analyses

Up to 24 individuals were to be randomized to achieve at least 16 evaluable participants who completed the study. Body sway and CPAB analyses were conducted using the completer analysis set, defined as all participants who had no major protocol deviations that would impact pharmacodynamic results, had sufficient pharmacodynamic data to derive at least one pharmacodynamic parameter, and who had completed all four treatment periods.

Inferential analyses were performed to evaluate treatment comparisons at each time point using a mixed-effect model with treatment, period, time point and the treatment × time point interaction as fixed effects, and participant as a random effect. For the evaluation of potential synergistic effects, period was removed from the model. Synergism was assessed to determine if the combined effects of alcohol and lemborexant were greater than the sum of the individual effects of alcohol and lemborexant (i.e. more than additive) and was based on the following contrast of means: lemborexant with alcohol − alcohol versus lemborexant − placebo. The primary treatment comparisons were for lemborexant coadministered with alcohol versus either lemborexant or alcohol alone. Alcohol alone was compared with placebo alone to demonstrate study validity, and lemborexant alone was compared with placebo as an exploratory analysis.

Pharmacokinetic analyses included all participants who received at least one dose of lemborexant and had sufficient data to derive at least one pharmacokinetic parameter. Concentration–time values below the limit of quantification were treated as zero up to the time at which the first quantifiable concentration was observed. Concentrations below the limit of quantification occurring after a measurable concentration in the concentration–time profile were also treated as zero. Pharmacokinetic parameters were calculated by noncompartmental analysis using Phoenix WinNonlin® version 8.0 (Princeton, NJ, USA). A linear mixed-effect analysis of variance was performed on the log-transformed

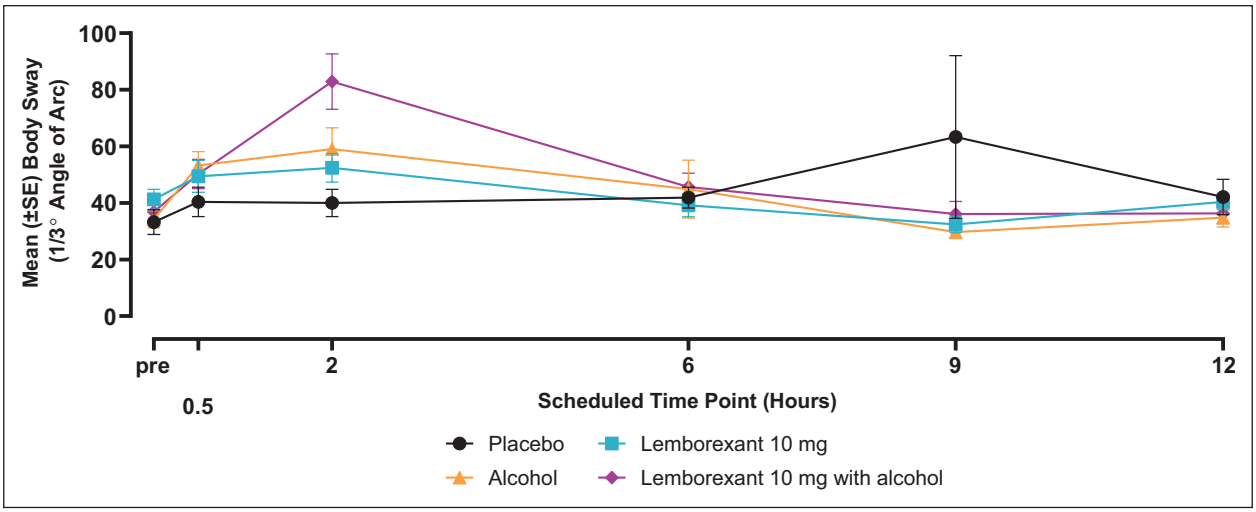

Figure 1. Mean body sway by time point and treatment (completer analysis set).
Pre: predose; SE: standard error.
Note: placebo refers to placebo for lemborexant with placebo for alcohol.

AUC_{0-72} and C_{max} values to evaluate the treatment effect of alcohol on lemborexant pharmacokinetics. Safety analyses included all individuals who received at least one dose of study treatment and had postdose safety data. All statistical analyses were performed using SAS version 9.4 (Cary, NC, USA).

Results

Participant disposition and baseline demographics

Overall, 121 participants underwent screening and 32 individuals were randomized to one of the four study treatment sequences (Supplemental Figure 1). Of the first 69 participants screened, 8 were randomized and 2 experienced AEs of syncope after blinded treatment and were discontinued; as a result, the study was halted and the protocol was amended to improve tolerability, including screening for orthostatic hypotension and giving a light breakfast prior to dosing. Due to implementation of the protocol amendment, the remaining 6 randomized individuals were discontinued for administrative reasons, and the remaining 61 screened individuals were classified as screen failures. Under the revised protocol, the additional 52 participants were screened and 24 participants were randomized. Of these 24 participants, 18 completed the study, and 6 were withdrawn by sponsor decision after the planned number of participants completed ($n=2$), AEs ($n=1$), physician decision ($n=1$), positive urine drug screen ($n=1$), and use of a prohibited concomitant medication (diphenhydramine hydrochloride 50 mg BID and betamethasone valerate 0.1% cream TID for insect bites; $n=1$). Therefore, in total, 32 participants were enrolled in the study, received at least one dose of randomized study treatment, and were analyzed for safety (safety analysis set). Of these 32 participants, 18 (56.3%) completed all four treatment periods in their assigned sequence and were included in the completer analysis set, and 28 (87.5%) participants were included in the pharmacokinetic analysis set.

Most participants were male (75.0%) and White (65.6%). Median age was 38.5 years (range = 26–54 years), and median body mass index was 27.2 kg/m² (range = 22.1–30.8 kg/m²).

Postural stability

The expected effect of alcohol was observed as a significantly greater increase from baseline in body sway at 2 h postdose when comparing alcohol alone versus placebo (least squares (LS) mean difference 23.7; $p<0.05$); no significant differences were observed at other time points (Table 1). No significant differences in change from baseline in body sway were seen for lemborexant alone versus placebo with the exception of the 9-h time point, when body sway was significantly worse in the placebo group compared with lemborexant alone. Sensitivity analysis suggested that the significant effect at the 9-h time point could likely be attributed to one individual in the placebo group with an unusually high body sway value. Lemborexant plus alcohol showed no statistically significant treatment difference versus alcohol alone at any time point. Lemborexant plus alcohol significantly increased body sway at 2 h postdose when compared with lemborexant alone (LS mean difference 36.2; $p<0.001$). By 12 h postdose, postural stability had generally returned to baseline values for all treatment groups (Figure 1). Although there was a significant period effect ($p<0.01$), it did not have a meaningful effect on the results reported since the treatments were balanced across periods and the LS means were adjusted for the effects in the model. There were no sequence effects in the model.

CPAB

Although there were significant period effects in the analysis for each of the parameters ($p<0.05$), they did not have meaningful effects on the results reported since the treatments were balanced across periods and the LS means were adjusted for the effects in the model. There were no sequence effects in the model. The change from baseline in power of attention was numerically increased (worsened) with alcohol alone versus placebo at the 0.5 and 2 h time points (Figure 2), although the treatment difference was not statistically significant (Table 2). Significant worsening in power of attention scores was seen at the 0.5 and 2 h time points with lemborexant alone versus placebo. Lemborexant plus

Table 1. Postural stability: treatment comparison of change from baseline for body sway (completer analysis set).[a]

Time point (h)	LEM10/alcohol vs alcohol	LEM10/alcohol vs LEM10	Alcohol vs placebo	LEM10 vs placebo	Synergy[b]
	Contrast mean difference (95% CI)				*p*-value
0.5	−5.4 (−22.8, 12.0)	6.8 (−10.6, 24.2)	13.0 (−4.4, 30.5)	0.8 (−16.6, 18.2)	0.598
2	16.8 (−1.7, 35.2)	36.2 (17.6, 54.7)***	23.7 (5.2, 42.2)*	4.3 (−14.2, 22.8)	0.395
6	−1.8 (−19.2, 15.6)	12.5 (−4.9, 29.9)	3.3 (−14.1, 20.7)	−10.9 (−28.3, 6.5)	0.481
9	3.9 (−13.5, 21.3)	9.7 (−7.8, 27.1)	−33.3 (−50.8, −15.9)**	−39.1 (−56.5, −21.7)**	<0.001[c]
12	−1.0 (−18.4, 16.4)	1.9 (−15.5, 19.4)	−7.0 (−24.4, 10.5)	−9.9 (−27.3, 7.5)	0.495
24	−0.4 (−18.4, 17.5)	11.5 (−6.5, 29.4)	−0.2 (−18.2, 17.7)	−12.1 (−30.1, 5.8)	0.371
48	−1.3 (−18.7, 16.1)	9.6 (−7.8, 27.0)	1.2 (−16.3, 18.6)	−9.8 (−27.2, 7.6)	0.517
72	4.1 (−13.3, 21.5)	11.6 (−5.9, 29.0)	−1.6 (−19.0, 15.9)	−9.1 (−26.5, 8.3)	0.308

CI: confidence interval; LEM10: lemborexant 10 mg.

[a]Body sway was measured in units of one-third degree of the angle of arc. Higher values indicate more body sway.

[b]Synergy comparison contrast: LEM10 with alcohol − alcohol versus LEM10 − placebo. The synergy effect of LEM10 with alcohol versus individual effects was evaluated from a mixed-effect model having treatment, time point and treatment by time point interaction as fixed effects, and participant as a random effect.

[c]Synergy effect was not statistically significant in sensitivity analysis which excluded one participant in the placebo group with an unusually high body sway value at the 9-h time point.

Note: placebo refers to placebo for LEM10 with placebo for alcohol.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

alcohol significantly worsened power of attention at 0.5 and 6 h postdose compared with lemborexant alone and at 0.5 and 2 h postdose compared with alcohol alone.

Alcohol resulted in a significantly greater reduction (worsening) from baseline in the continuity of attention composite score compared with placebo at 2 h postdose (Figure 2 and Table 2). A significant worsening at 2 h postdose was also seen with lemborexant alone versus placebo. Lemborexant plus alcohol significantly worsened continuity of attention composite scores at 2 h postdose compared with lemborexant alone and at 0.5, 2, and 6 h postdose versus alcohol alone.

For the quality of memory domain, significantly greater reductions (worsening) from baseline were seen at 0.5 and 2 h postdose for each active substance alone versus placebo (Figure 2 and Table 2). Significant worsening was also observed with lemborexant plus alcohol at 0.5 and 2 h postdose when compared with lemborexant alone and at 2 h postdose only versus alcohol alone.

No significant increase (worsening) of speed of memory retrieval domain scores was seen with alcohol alone compared with placebo (Figure 2 and Table 2). Speed of memory retrieval domain scores were significantly worsened at the 0.5- and 2-h time points with lemborexant alone versus placebo. Lemborexant plus alcohol significantly worsened speed of memory retrieval at 2 h postdose when compared with lemborexant alone and at 0.5, 2, and 6 h postdose when compared with alcohol alone.

Overall, no statistically significant treatment differences in change from baseline were observed at 9 h or later time points for any of the four cognitive performance domains. There were no statistically significant synergistic effects for an alcohol interaction at any time point for any of the domains.

Pharmacokinetics

Pharmacokinetic parameters of lemborexant administered with or without alcohol are summarized in Table 3. Median lemborexant t_{max} was 1.5 h when administered with alcohol and 1.7 h when lemborexant was administered alone. Mean C_{max} was 35% higher with lemborexant plus alcohol compared with lemborexant alone (geometric mean ratio (90% confidence interval (CI)) = 135.1 (114.2, 159.8)). Coadministration of lemborexant with alcohol resulted in a 70% increase in overall lemborexant exposure, based on AUC_{0-72}, when compared with lemborexant alone (geometric mean ratio (90% CI) = 170.5 (153.6, 189.3)). Apparent clearance (CL/F) of lemborexant was lower when lemborexant was coadministered with alcohol (27.83 L/h) versus lemborexant alone (39.99 L/h). Plasma concentrations of lemborexant were low at 9 h and later time points and were similar for lemborexant administered with or without alcohol (Figure 3). The lemborexant metabolites, M4, M9, and M10, showed a decrease in C_{max} of 17–33% when lemborexant was coadministered with alcohol (Table 3). Based on AUC from time 0 to 9 h (AUC_{0-9}), M4 and M10 metabolite exposure was decreased with lemborexant plus alcohol, but M9 metabolite exposure was similar with and without alcohol coadministration. At 72 h postdose, M4 and M10 exposures were similar with and without alcohol coadministration, but exposure to the M9 metabolite was increased by approximately 26% with alcohol (Table 3; Supplemental Figure 2). Mean (standard deviation) blood alcohol levels were similar for alcohol alone and for alcohol with lemborexant as assessed at 0.5 h postdose (766 (189) µg/mL and 706 (367) µg/mL, respectively) and at 2 h postdose (890 (123) µg/mL and 800 (162) µg/mL, respectively).

Safety

The incidence of treatment–emergent adverse events (TEAEs) was lower with placebo (33.3%) compared with lemborexant alone (96.2%), lemborexant plus alcohol (95.2%), and alcohol alone (83.3%) (Table 4). Three participants experienced TEAEs leading to study discontinuation following administration of alcohol alone (mild nausea, $n = 1$; moderate vomiting, $n = 1$) or lemborexant plus alcohol (mild muscle weakness, $n = 1$). There were no serious TEAEs and most TEAEs were mild. One individual (49-year-old African American male) experienced a severe TEAE of syncope following administration of alcohol alone that resolved following administration of intravenous sodium chloride. Across the treatment groups, somnolence was the most

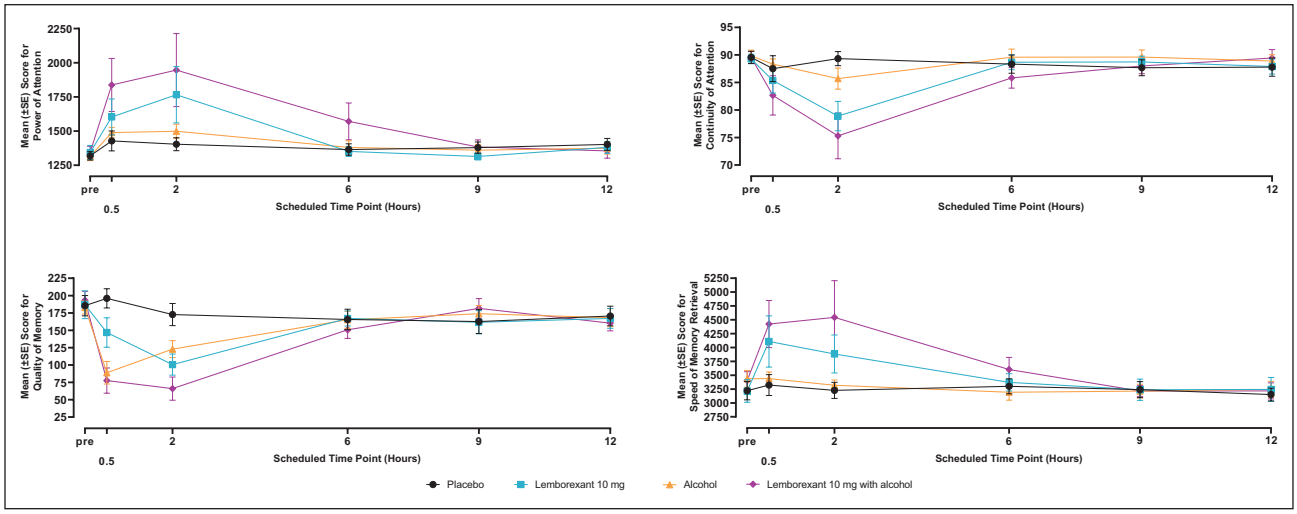

Figure 2. Mean cognitive performance domain scores by time point and treatment (completer analysis set).
Pre: predose; SE: standard error.
Note: placebo refers to placebo for lemborexant with placebo for alcohol.

common TEAE (placebo, 12.5%; alcohol alone, 37.5%; lemborexant alone, 88.5%; lemborexant plus alcohol, 85.7%) (Table 4). There were no trends of clinical concern for vital signs, electrocardiograms, blood chemistry, hematology, and urinalysis.

Discussion

This Phase 1, double-blind, placebo-controlled study assessed the effects of concomitant administration of single doses of lemborexant 10 mg with alcohol on postural stability and cognitive performance in healthy adults. The alcohol dose, equivalent to three standard alcohol-containing drinks, increased mean blood alcohol levels to above 800 µg/mL (0.08%), the US federal standard for alcohol intoxication. Lemborexant administered with alcohol did not show evidence of additivity on postural stability compared with alcohol alone. However, the coadministration of lemborexant with alcohol showed additive negative effects on cognitive performance measures, which corresponded with the approximate time of peak plasma lemborexant concentrations (mean t_{max} = 1.5 h), and then resolved over time. Pharmacokinetic analyses indicated an increase in exposure to lemborexant when coadministered with alcohol. Based on these findings, patients are advised not to consume alcohol with lemborexant.

The validity of the study was supported by the significant worsening effect of alcohol alone on postural stability seen at 2 h after dosing. Alcohol alone also significantly worsened continuity of attention and quality of memory measures on the CPAB, and the numerical changes in power of attention and speed of memory retrieval were consistent with an alcohol-related worsening of cognitive performance. The addition of alcohol to lemborexant also worsened postural stability and cognitive performance when compared with lemborexant alone, which could be attributed to the effect of alcohol.

The primary cognitive assessment of interest was the change from baseline in the power of attention battery, which measures the ability to focus attention and process information, and has been shown to be sensitive to the impairing effects of alcohol (van Harten et al., 1992; Wesnes et al., 2000). Given its intentional sleep-promoting pharmacologic effects, it was not unexpected that lemborexant alone or when combined with alcohol resulted in significant changes from baseline in the power of attention assessment as well as in the domains of continuity of attention, quality of memory, and speed of memory retrieval at 2 h after dosing. Per the recommended dosing regimen, lemborexant is taken immediately before going to bed and has a t_{max} of approximately 1–3 h (Landry et al., 2021c). In healthy subjects, lemborexant 10 mg significantly impaired cognitive performance in the middle of the night (approximately 4 h after dosing), as assessed by the CPAB, with no impairments observed the next morning (Moline et al., 2021; Murphy et al., 2020). It is noteworthy that, in this study, any negative effects on cognitive performance had resolved by 6–9 h after dosing, which roughly corresponds with a normal wake time following a night's sleep. These results are consistent with the findings for other DORAs, including suvorexant, almorexant, and daridorexant, which demonstrated that peak psychomotor and/or cognitive impairments observed with the DORA alone, or in combination with alcohol, typically occurred around t_{max} and resolved over time (Berger et al., 2020; Hoch et al., 2013; Sun et al., 2015).

The pharmacokinetics of lemborexant in healthy subjects have been well defined in the previous studies (Landry et al., 2021c). Lemborexant is primarily metabolized by cytochrome P450 (CYP)3A4 (Landry et al., 2021a). Of the major lemborexant metabolites (M4, M9, and M10), none has been shown to be pharmacologically active (Ueno et al., 2021). The M4, M9, and M10 metabolites bind orexin receptors with similar affinities to that of lemborexant, but, unlike lemborexant, the metabolites are good P-glycoprotein substrates, limiting their brain penetration and subsequent pharmacologic activity (Ueno et al., 2021).

Concomitant administration with alcohol resulted in increased exposure to lemborexant, with a 35% increase in C_{max}, and a decrease in apparent clearance. Although there was a 70% increase in $AUC_{0–72}$, plasma lemborexant concentrations were

Table 2. Cognitive performance: treatment comparison of each CPAB domain change from baseline (completer analysis set).

Time point (h)	LEM10/alcohol vs alcohol	LEM10/alcohol vs LEM10	Alcohol vs placebo	LEM10 vs placebo	Synergy[b]
	Contrast mean difference (95% CI)				*p*-value
Power of attention[a]					
0.5	346.5 (131.1, 561.9)**	239.2 (23.3, 455.2)*	132.1 (−83.9, 348.0)	239.3 (23.9, 454.8)*	0.469
2	469.3 (246.6, 692.0)***	165.5 (−57.8, 388.9)	127.4 (−95.9, 350.8)	431.2 (208.5, 653.9)***	0.813
6	170.2 (−38.5, 378.9)	234.7 (25.8, 443.6)*	30.4 (−178.5, 239.3)	−34.0 (−242.8, 174.7)	0.152
9	−9.4 (−212.3, 193.4)	73.1 (−129.9, 276.2)	−3.4 (−206.5, 199.6)	−86.0 (−288.8, 116.8)	0.573
12	−51.8 (−254.6, 151.1)	−21.6 (−224.7, 181.4)	−13.1 (−216.1, 190.0)	−43.2 (−246.1, 159.6)	0.985
24	−96.8 (−299.6, 106.1)	−6.3 (−209.4, 196.7)	19.3 (−183.7, 222.4)	−71.2 (−274.0, 131.7)	0.893
48	−33.9 (−236.7, 168.9)	−34.8 (−237.9, 168.2)	−46.0 (−249.1, 157.0)	−45.1 (−247.9, 157.7)	0.907
72	7.9 (−194.9, 210.7)	28.6 (−174.4, 231.7)	1.6 (−201.4, 204.7)	−19.1 (−221.9, 183.7)	0.822
Continuity of attention[c]					
0.5	−3.72 (−7.42, −0.01)*	−1.90 (−5.61, 1.82)	−0.96 (−4.68, 2.75)	−2.78 (−6.49, 0.93)	0.845
2	−10.81 (−14.64, −6.98)***	−5.96 (−9.81, −2.12)**	−4.93 (−8.77, −1.08)*	−9.78 (−13.61, −5.94)***	0.875
6	−3.61 (−7.2, −0.02)*	−3.44 (−7.03, 0.16)	0.86 (−2.74, 4.45)	0.68 (−2.91, 4.27)	0.095
9	−1.45 (−4.94, 2.04)	−1.29 (−4.78, 2.20)	1.61 (−1.88, 5.11)	1.45 (−2.04, 4.94)	0.270
12	0.72 (−2.77, 4.21)	1.00 (−2.50, 4.49)	0.78 (−2.71, 4.27)	0.51 (−2.99, 3.99)	0.855
24	1.55 (−1.94, 5.04)	−0.29 (−3.78, 3.21)	−0.28 (−3.77, 3.21)	1.56 (−1.93, 5.05)	0.928
48	0.94 (−2.55, 4.43)	−0.67 (−4.17, 2.82)	−1.94 (−5.44, 1.55)	−0.33 (−3.82, 3.16)	0.537
72	1.27 (−2.22, 4.76)	−0.90 (−4.39, 2.60)	−3.22 (−6.71, 0.28)	−1.05 (−4.54, 2.44)	0.294
Quality of memory[c]					
0.5	−20.35 (−55.91, 15.21)	−67.69 (−103.33, −32.05)***	−102.46 (−138.10, −66.82)***	−55.12 (−90.68, −19.57)**	0.101
2	−77.80 (−114.56, −41.04)***	−46.84 (−83.71, −9.97)*	−47.15 (−84.02, −10.28)*	−78.11 (−114.86, −41.35)***	0.801
6	−26.50 (−60.95, 7.95)	−28.43 (−62.91, 6.05)	−1.36 (−35.85, 33.12)	0.57 (−33.89, 35.02)	0.185
9	−2.94 (−36.42, 30.54)	9.45 (−24.06, 42.97)	10.23 (−23.29, 43.74)	−2.16 (−35.64, 31.32)	0.987
12	−18.34 (−51.82, 15.14)	−17.39 (−50.91, 16.13)	−3.60 (−37.12, 29.91)	−4.55 (−38.034, 28.93)	0.532
24	−15.98 (−49.46, 17.50)	−13.94 (−47.46, 19.57)	1.09 (−32.42, 34.61)	−0.95 (−34.43, 32.53)	0.495
48	−27.15 (−60.63, 6.33)	−19.76 (−53.28, 13.76)	7.47 (−26.05, 40.98)	0.07 (−33.41, 33.55)	0.211
72	−19.59 (−53.07, 13.89)	−15.83 (−49.35, 17.68)	12.13 (−21.39, 45.64)	8.37 (−25.11, 41.85)	0.198
Speed of memory retrieval[a]					
0.5	959.9 (491.4, 1428.4)***	4.2 (−465.5, 473.8)	−32.3 (−502.0, 437.3)	923.4 (454.9, 1391.9)***	0.928
2	1227.3 (743.0, 1711.6)***	638.6 (152.8, 1124.4)*	17.4 (−468.4, 503.2)	606.1 (121.8, 1090.5)*	0.129
6	495.5 (41.5, 949.5)*	92.6 (−361.7, 547.0)	−340.9 (−795.3, 113.4)	61.9 (−392.1, 515.9)	0.189
9	49.6 (−391.5, 490.8)	−160.3 (−601.9, 281.4)	−222.4 (−664.0, 219.2)	−12.5 (−453.7, 428.6)	0.925
12	24.3 (−416.9, 465.5)	−161.8 (−603.4, 279.9)	−105.9 (−547.5, 335.7)	80.2 (−361.0, 521.3)	0.778
24	−12.5 (−453.6, 428.7)	−282.6 (−724.3, 159.0)	−267.3 (−709.0, 174.3)	2.8 (−438.3, 444.0)	0.879
48	198.9 (−242.3, 640.1)	−127.4 (−569.0, 314.3)	−378.5 (−820.1, 63.1)	−52.2 (−493.4, 388.9)	0.485
72	−7.4 (−448.6, 433.7)	−109.8 (−551.4, 331.9)	−153.1 (−594.7, 288.6)	−50.7 (−491.9, 390.4)	0.972

CI: confidence interval; CPAB: cognitive performance assessment battery; LEM10: lemborexant 10 mg.

[a]Composite score units are ms. Lower values indicate a faster (better) performance.

[b]Synergy comparison contrast: LEM10 with alcohol – alcohol versus LEM10 – placebo. The synergy effect of LEM10 with alcohol versus individual effects was evaluated from a mixed-effect model having treatment, time point and treatment by time point interaction as fixed effects, and participant as a random effect.

[c]Composite scores are unitless (null). Higher values indicate a better performance.

Note: placebo refers to placebo for LEM10 with placebo for alcohol.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

low by 9 h postdose and similar for lemborexant with and without alcohol. This is consistent with the absence of negative effects on cognitive performance and postural stability seen at 9 h postdose. Coadministration with alcohol has also been shown to increase exposure to almorexant by 21% (Hoch et al., 2013) but did not increase exposure to daridorexant or suvorexant (Berger et al., 2020; Sun et al., 2015). Alcohol has been reported to increase t_{max} for daridorexant by approximately 1.25 h (Berger et al., 2020) but did not increase t_{max} for almorexant (Hoch et al., 2013) or suvorexant (Sun et al., 2015), which is consistent with the lack of increase in t_{max} for lemborexant in this study. The mechanism underlying the effects of alcohol on lemborexant exposure has not been established; however, alcohol has been shown to impact the pharmacokinetics of other drug substances by various mechanisms, including altering the rate of absorption, the total amount of drug substance absorbed, or modifying drug clearance (Chan and Anderson, 2014). The effects of alcohol on the pharmacokinetic properties of lemborexant may have contributed to the observed additive pharmacodynamic effects on cognitive performance.

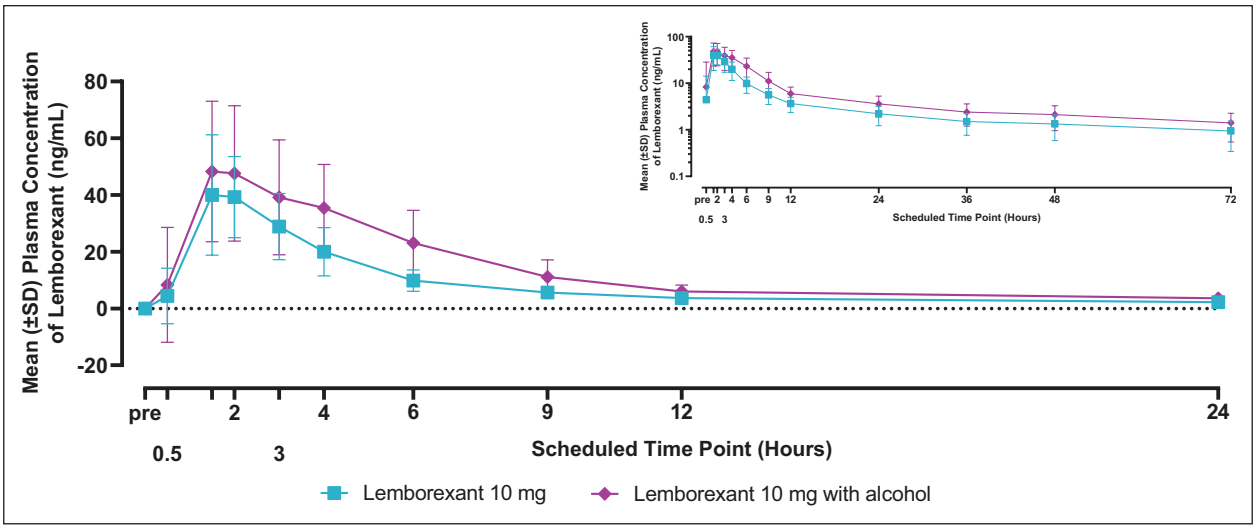

Figure 3. Mean plasma concentration of lemborexant (pharmacokinetic analysis set).
Pre: predose; SD: standard deviation.

Table 3. Summary of pharmacokinetic parameters for lemborexant and the M4, M9, and M10 metabolites (pharmacokinetic analysis set).

PK parameter	LEM10 alone ($n=24$)	LEM10/alcohol ($n=18$)[a]	Geometric mean ratio (90% CI)
Lemborexant			
t_{max}, (h)[b]	1.7 (0.4, 3.0)	1.5 (0.4, 5.9)	–
C_{max}, ng/mL			
Geometric mean (% CV)	45.2 (31.1)	58.1 (33.2)	135.1 (114.2, 159.8)
Mean (SD)	47.3 (15.3)	60.8 (18.1)	–
AUC_{0-9}, ng h/mL			
Geometric mean (% CV)	145.1 (33.2)	231.5 (29.3)	166.2 (146.3, 188.8)
Mean (SD)	152.3 (46.9)	240.9 (72.4)	–
AUC_{0-72}, ng h/mL			
Geometric mean (% CV)	250.0 (40.6)	402.3 (35.2)	170.5 (153.6, 189.3)
Mean (SD)	267.8 (96.5)	425.3 (147.3)	–
$t_{½}$, (h)			
Mean (SD)	33.9 (7.9)	29.9 (7.1)	–
M4			
t_{max}, (h)[b]	3.0 (1.5, 4.0)	4.0 (3.0, 8.9)	–
C_{max}, ng/mL			
Geometric mean (% CV)	9.8 (24.7)	6.4 (31.6)	66.6 (59.8, 74.3)
Mean (SD)	10.1 (2.6)	6.7 (2.3)	–
AUC_{0-9}, ng h/mL			
Geometric mean (% CV)	56.0 (20.4)	39.6 (31.8)	71.0 (62.8, 80.3)
Mean (SD)	57.1 (11.8)	41.4 (13.4)	–
AUC_{0-72}, ng h/mL			
Geometric mean (% CV)	124.3 (32.8)	125.5 (29.1)	107.3 (98.0, 117.5)
Mean (SD)	130.5 (41.2)	130.5 (38.2)	–
$t_{½}$, (h)			
Mean (SD)	24.1 (4.8)	26.5 (5.8)	–
M9			
t_{max}, (h)[b]	1.9 (1.5, 3.0)	4.0 (1.9, 5.9)	–
C_{max}, ng/mL			
Geometric mean (% CV)	6.4 (30.9)	5.1 (28.2)	82.6 (72.0, 94.7)
Mean (SD)	6.7 (2.4)	5.3 (1.5)	–

(Continued)

Table 3. (Continued)

PK parameter	LEM10 alone ($n=24$)	LEM10/alcohol ($n=18$)[a]	Geometric mean ratio (90% CI)
AUC_{0-9}, ng h/mL			
Geometric mean (% CV)	24.9 (26.9)	26.4 (24.4)	108.9 (94.8, 125.0)
Mean (SD)	25.7 (7.5)	27.1 (6.4)	–
AUC_{0-72}, ng h/mL			
Geometric mean (% CV)	54.5 (31.8)	65.1 (20.9)	126.1 (114.3, 139.1)
Mean (SD)	57.1 (18.9)	66.3 (12.8)	–
$t_{½}$, (h)			
Mean (SD)	24.7 (8.2)	26.0 (6.5)	–
M10			
t_{max}, (h)[b]	4.0 (1.9, 5.9)	5.9 (4.0, 24.0)	–
C_{max}, ng/mL			
Geometric mean (% CV)	4.7 (23.9)	3.3 (29.4)	71.4 (64.5, 78.9)
Mean (SD)	4.8 (1.1)	3.4 (1.1)	–
AUC_{0-9}, ng h/mL			
Geometric mean (% CV)	29.9 (24.2)	19.6 (35.0)	64.9 (56.7, 74.2)
Mean (SD)	30.7 (6.6)	20.7 (7.4)	–
AUC_{0-72}, ng h/mL			
Geometric mean (% CV)	140.2 (26.4)	127.2 (27.5)	94.1 (85.9, 103.1)
Mean (SD)	144.7 (37.0)	131.9 (39.4)	–
$t_{½}$, (h)			
Mean (SD)	30.1 (11.6)	35.8 (10.8)	–

AUC_{0-9}: area under the plasma concentration–time curve from time 0–9 h; AUC_{0-72}: area under the plasma concentration–time curve from time 0–72 h; C_{max}: maximum observed plasma concentration; CV: coefficient of variation; LEM10: lemborexant 10 mg; $t_{½}$: elimination half-life; t_{max}: time to reach C_{max} after dosing.
[a]Data from one participant in the lemborexant 10 mg with alcohol group had to be excluded from the pharmacokinetic analysis due to vomiting within 2 h postdose.
[b]Data shown are the median (range).

Table 4. Summary of treatment–emergent adverse events (safety analysis set).

	Placebo ($n=24$)	LEM10 ($n=26$)	Alcohol ($n=24$)	LEM10/alcohol ($n=21$)
Participants with ⩾1 TEAE, *n* (%)[a]	8 (33.3)	25 (96.2)	20 (83.3)	20 (95.2)
TEAEs reported for >2 participants in any group, *n* (%)				
Somnolence	3 (12.5)	23 (88.5)	9 (37.5)	18 (85.7)
Headache	0	2 (7.7)	7 (29.2)	4 (19.0)
Dizziness	1 (4.2)	0	5 (20.8)	5 (23.8)
Fatigue	3 (12.5)	1 (3.8)	1 (4.2)	4 (19.0)
Feeling drunk	0	0	4 (16.7)	4 (19.0)
Nausea	0	0	3 (12.5)	5 (23.8)
Vomiting	0	0	3 (12.5)	2 (9.5)
Euphoric mood	0	0	3 (12.5)	1 (4.8)

LEM10: lemborexant 10 mg; TEAE: treatment–emergent adverse event.
[a]TEAE starting or worsening after the study treatment.

Most TEAEs were mild in severity and the TEAE profile was similar to the findings from lemborexant randomized clinical trials (Kärppä et al., 2020; Murphy et al., 2017; Rosenberg et al., 2019). Consistent with its intended clinical use as a sleep-promoting agent, the most commonly reported TEAE for lemborexant was somnolence, and was not unexpected given the morning dosing regimen.

The four-way crossover design was employed to reduce the influence of confounding covariates and prevent an order effect. The standard 14-day washout period between treatments used in this study and other lemborexant studies was sufficient to avoid carryover effects. Enrolled individuals were current occasional or regular alcohol users to improve the likelihood that individuals would be able to tolerate drinking the equivalent of three standard alcoholic drinks in the morning. Limitations of the study were the high dropout rate which may have been partly because of the length of the study. The inability to fully blind the randomized treatment assignment because of the distinctive taste and smell of alcohol is an issue common to studies of this kind. Another limitation of the study was that dosing occurred in the morning, which is likely not the time of day when alcohol and sleep-promoting drugs would be used concomitantly.

Conclusion

Lemborexant 10 mg did not impair postural stability when administered alone, and did not worsen the negative effects of alcohol on postural stability. Alcohol alone and lemborexant alone worsened cognitive domain scores, and coadministration of lemborexant with alcohol showed additive negative effects on cognitive performance. Coadministration with alcohol increased peak and overall lemborexant exposure, and this increased exposure may have contributed in part to the additive negative effects observed on cognitive measures. Overall, this study suggests that lemborexant should not be taken with alcohol.

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Author contributions

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. I.L., J.A., B.S., N.H., and M.M. were involved in the study design. I.L., J.A., and S.D. were involved in data collection, and I.L., J.A., B.S., S.D., N.H., and M.M. in the data interpretation.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: N.H., J.A., S.D., L.R., and M.M. are the employees of Eisai Inc. or Eisai Co., Ltd. I.L. and G.F. are former employees of Eisai Inc. B.S. is affiliated with Syneos Health, Raleigh, NC, USA, and Department of Toxicology and Pharmacology, University of Toronto, Toronto, Canada.

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Eisai Inc. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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