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Effects of Lemborexant on the Pharmacokinetics of Oral Contraceptives: Results From a Phase 1 Drug-Drug Interaction Study in Healthy Females

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Lemborexant is a dual orexin receptor antagonist approved in multiple countries including the United States, Canada, and Japan for the treatment of insomnia in adults. As women of childbearing potential may be prescribed insomnia drugs, a drug-drug interaction study was conducted. This single-center, open-label, fixed-sequence study examined potential drug-drug interactions between lemborexant and an oral contraceptive (OC) in healthy females (18–44 years, n = 20). The purpose of this study was to determine the effect of lemborexant 10 mg (at steady state) on the pharmacokinetics of a single dose of OC (0.03 mg ethinyl estradiol and 1.5 mg norethindrone acetate), assess the effect of a single dose of OC on lemborexant pharmacokinetics, and evaluate safety and tolerability of lemborexant and OC coadministration. Ethinyl estradiol maximum plasma drug concentration was not altered by lemborexant coadministration; area under the curve from zero time to the last quantifiable concentration was slightly increased, by 13%. No clinically relevant effects on norethindrone acetate pharmacokinetics were observed. Coadministration of OC with lemborexant had no clinically relevant effect on the steady-state pharmacokinetics of lemborexant. Adverse events were consistent with the known safety profile. These results support the conclusion that lemborexant and OC can be coadministered without dose adjustment.

Keywords

lemborexant, oral contraceptives, insomnia, pharmacokinetics, dual orexin receptor antagonist

Lemborexant is a dual orexin receptor antagonist approved in multiple countries including the United States, Canada, and Japan for the treatment of insomnia and is being explored as a treatment for irregular sleep-wake rhythm disorder.[1,2] Improvements in sleep onset and sleep maintenance parameters were observed with lemborexant compared with placebo for 1 and 6 months, respectively, in the phase 3 pivotal studies of lemborexant for insomnia (Study 304 [SUNRISE-1; NCT02783729; E2006-G000-304] and Study 303 [SUNRISE-2; NCT02952820; E2006-G000-303]).[2,3] Lemborexant was well tolerated in both studies.

Many women are prescribed an oral contraceptive (OC)[4] for contraceptive and noncontraceptive purposes. The most common method of contraception in the United States is OC.[5] The use of OC is also recommended in the management of polycystic ovarian syndrome.[6] As OCs are so commonly prescribed, it is likely that an OC will be coadministered with lemborexant in women of reproductive age. Among the most commonly used OCs are those that contain both ethinyl estradiol (EE) and synthetic progestin, such as norethindrone acetate (NE).[7] Although there is no mechanistic basis to predict drug-drug interactions (DDIs), this study was conducted to formally assess

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potential DDIs between an OC and lemborexant when coadministered. The current study (NCT03451110; E2006-A001-012) examined possible DDIs between lemborexant and a commonly prescribed OC, Loestrin®, in the combination formulation of 0.03 mg EE/1.5 mg NE.

EE is typically prescribed at low doses. Systemic exposure to EE (<10 nmol/L) is also very low.[8] Although EE has demonstrated a low potential for clinically significant DDIs with several medications,[9,10] clinically significant interactions have been reported with certain drugs, including ritonavir, carbamazepine, phenytoin, phenobarbital, and rifampicin.[4,11,12] EE is a substrate for a number of enzymes involved in drug metabolism (SULT1E1, UGT1A1, CYP3A4, and CYP2C9) and inhibits other enzymes, such as cytochrome P450 (CYP) isoforms.[8]

EE is metabolized mainly through sulfation and hydroxylated by CYP3A[13] and glucuronidated.[8,14] NE is primarily metabolized by CYP3A,[15] sulfotransferases, and uridine 5-diphospho-glucoronosyltransferase. Lemborexant is also primarily metabolized by CYP3A, as shown by in vitro studies.[16,17] CYP3A is among the most important CYP isoforms with a role in drug metabolism by humans because it is the major enzyme of its type in crucial tissues such as the gastrointestinal tract and liver.[18] Based on nonclinical data, lemborexant is not a CYP3A inhibitor, although in vitro data indicated a potential to both inhibit and induce CYP3A and CYP2B6.[13] At clinically relevant concentrations, lemborexant is neither an inducer nor a significant inhibitor of CYP3A as shown by the DDI study conducted with midazolam, a sensitive CYP3A substrate.[19] The key metabolites of lemborexant are M4, M9, and M10[20] (all P-glycoprotein substrates), with M10 being the most abundant. These metabolites have a similar binding affinity for orexin receptors as lemborexant. However, the influence of M4, M9, and M10 on the pharmacological activity of lemborexant is believed to be minimal because of the lack of P-glycoprotein brain penetration of the metabolites.[17,21] Based on this information, the likelihood of an interaction was considered minimal.

Although lemborexant showed no effect on the exposure of a sensitive CYP3A substrate (midazolam), given the complex metabolism of EE and NE, a DDI study was conducted to confirm lemborexant has no effect on their exposures. The purpose of the current study was to examine the effect of lemborexant on the pharmacokinetics (PK) of a single dose of OC, to examine the effect of a single dose of OC on lemborexant PK, and to evaluate the safety and tolerability of lemborexant in women of childbearing potential who coadminister OC.

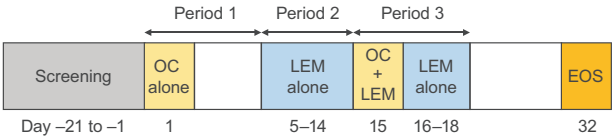

Figure 1. Overview of study design. EOS, end of study; LEM, lemborexant; OC, oral contraceptive.

Materials and Methods

Study Participants

Subjects participating in this study were healthy females aged 18-44 years old at the time of screening. Subjects must not have used any form of hormonal contraceptive, including a hormonal intrauterine device, for a minimum of 8 weeks prior to dosing. This would allow for understanding the effect of a single dose of OC on lemborexant at steady state. All subjects had to be willing and able to comply with all aspects of the study protocol and to provide written informed consent. Exclusion criteria included any known contraindication to EE/NE-based OCs, breastfeeding, pregnancy, and nonadherence to approved nonhormonal contraception methods in the 28 days prior to starting the study and for 28 days after discontinuation of the study drug.

Study Design

This was a single-center, open-label, fixed-sequence DDI study conducted at 1 site (Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, Texas) in the United States. The study was approved by an institutional review board (IntegReview Independent Review Board, Austin, Texas) and followed principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Declaration of Helsinki. Informed consent was obtained in writing from all subjects prior to any screening procedures.

This study was composed of 2 phases: prerandomization and treatment. The prerandomization phase consisted of screening and baseline, during which time subjects were assessed for meeting study criteria, and baseline assessment measurements were obtained. Subjects meeting inclusion criteria proceeded to the 3-period treatment phase (Figure 1).

In period 1, subjects were administered a single dose of the OC (0.03 mg EE and 1.5 mg NE) on the evening of day 1 approximately 5 minutes prior to the scheduled bedtime following a fast of ≥3 hours. Both these hormones are well-known active ingredients of several approved OCs.[7]

During period 2, subjects were administered lemborexant 10 mg for 10 days starting on day 5

in the evening following the last OC PK sample. During period 3, lemborexant 10 mg was administered in the evening on days 15-18. On day 15, a single dose of OC was coadministered with lemborexant following a ≥3-hour fast (approximately 5 minutes prior to scheduled bedtime). Each subject had a follow-up visit approximately 14 days (day 32) after the last lemborexant dose (day 18).

Blood samples (4 mL per time point) were collected at predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, and 96 hours postdose for determining plasma concentrations of EE and NE on days 1 and 15. Blood samples (4 mL per time point) to determine predose plasma concentrations of lemborexant and its metabolites (M4, M9, M10) were obtained predose on days 11, 12, and 13 to confirm lemborexant at steady state. Blood samples for determination of a complete lemborexant PK profile with or without OC coadministration were taken on day 14 and on day 15 at predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

Bioanalytical Methods and PK Assessments

Plasma concentrations of EE, NE, and lemborexant were measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Blood samples (4 mL each) were collected with K_2-ethylenediaminetetraacetic acid as anticoagulant for the assessment of EE and NE PK. EE and NE were extracted from 300 μL of human plasma by a liquid-liquid extraction technique using 50/50 acetonitrile (ACN)/water and extracted with methyl tertiary butyl ether (MTBE). The MTBE layer was evaporated under a nitrogen stream and reconstituted with $NaHCO_3$ and dansyl chloride in ACN and then incubated for 3 minutes at 60°C. EE and NE were extracted again with MTBE followed by evaporation of the organic layer and reconstituted again with 50/50 ACN/water prior to LC-MS/MS analysis. The LC-MS/MS analysis was carried out with a Sciex API-5500 Triple Quad mass spectrometer coupled with a Shimadzu LC system (Phenomenex Kinetex FS 2.6 μm, 100 × 2.1 mm chromatography column, with a mobile-phase gradient). The mass spectrometer was operated in positive electrospray ionization mode, and resolution setting used was unit for both Q1 and Q3. The multiple reaction monitoring (MRM) transition was mass-to-charge ratio (*m*/*z*) 530.4→171.1 for EE and *m*/*z* 534.4→171.2 for NE. The MRM transition was *m*/*z* 299.3→231.1 and *m*/*z* 305.2→237.2 for the deuterated internal standard EE-d_4 and NE-d_6, respectively. The lower limit of quantitation for EE was 10.0 pg/mL with a calibration range of 10.0-2000 pg/mL. The lower limit of quantitation for NE was 100 pg/mL with a calibration range of 100-20,000 pg/mL. The option to dilute samples originally above the upper limit of the calibration range was validated by analyzing 6 replicate quality controls at 10-fold dilutions. The validated method had interday and intraday precision and accuracy of less than 12.3% for EE and NE and less than 18.0% at the lower limit of quantification for EE, with incurred sample reanalysis passing the criteria in study samples. Appropriate bioanalytical noninterference of coadministered compounds was demonstrated before study sample analysis. Long-term stability was established up to 133 days in frozen human plasma at −70°C.

Blood samples (4 mL each) were collected with sodium heparin as anticoagulant for the PK assessment of lemborexant and its metabolites, M4, M9, and M10. Lemborexant and its metabolites were extracted from 100 μL of human plasma by a liquid-liquid extraction technique. Samples were diluted with 0.1% formic acid in 50/50 ACN/water. Ammonium hydroxide was added, and samples were then extracted with MTBE. The MTBE layer was evaporated under a nitrogen stream and reconstituted with 0.1% formic acid in 50/50 ACN/water prior to LC-MS/MS analysis. The LC-MS/MS analysis was carried out with a Sciex API-5500 Triple Quad mass spectrometer coupled with a Shimadzu LC system (Phenomenex Kinetex, 5μm XB-C18, 100A, chromatography column, 250 × 4.6 mm, with a mobile-phase gradient). The mass spectrometer was operated in positive electrospray ionization mode, and resolution setting used was unit for both Q1 and Q3. The MRM transition was *m*/*z* 411.0→287.1 for lemborexant and *m*/*z* 427.0→287.1 for M4, M9, and M10. The MRM transition was *m*/*z* 414.0→290.1 for the deuterated internal standard lemborexant-d_3 and *m*/*z* 414.0→290.1 for M4-d_3, M9-d_3, and M10-d_3. For all analytes, the lower limit of quantitation was 0.0500 ng/mL, and the calibration curve ranged from 0.0500 to 50.0 ng/mL. The option to dilute samples originally above the upper limit of the calibration range was validated by analyzing 6 replicate quality controls containing 500 ng/mL lemborexant as 10-fold dilutions. The validated method had interday and intraday precision and accuracy of less than 14.7% across all analytes, with incurred sample reanalysis passing the criteria in study samples. Appropriate bioanalytical noninterference of coadministered compounds was demonstrated before study sample analysis. Long-term stability was established up to 34 months in frozen human plasma at −70°C.

The PK parameter endpoints included area under the plasma concentration-time curve from zero time to 24 hours postdose ($AUC_{0\text{-}24h}$), maximum plasma drug concentration (C_{max}), time to reach maximum plasma drug concentration (t_{max}), and predose concentration (C_{min}) for lemborexant; and AUC from zero time to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$),

AUC from zero time extrapolated to infinity ($AUC_{0\text{-inf}}$), C_{max}, and t_{max} for NE and EE.

Safety Assessments

Safety assessments included reports of treatment-emergent adverse events (TEAEs), vital signs, weight, electrocardiograms, physical exams, clinical laboratory evaluations, and suicidality. All adverse events, regardless of relationship to the study drug or procedure, were collected from the time of the signing of the informed consent form until the last visit of the treatment phase and for 28 days after the last dose. Adverse events were followed for 28 days or until resolution, whichever occurred first.

Statistical Methods

The number of subjects enrolled was based on the number estimated to provide at least 90% power to demonstrate equivalence in exposure to synthetic EE and NE components of the OC in the presence and absence of lemborexant.

Estimates of within-subject variability were derived from published PK studies of OC brands. Reported within-subject coefficients of variation typically ranged between 10% and 20%. These calculations assumed a normal distribution of log (C_{max}) and log (AUC_{tau}), where tau is the dosing interval of EE and NE with intrasubject coefficients of variation of a maximum of 21.4% and 15.5%, respectively, for EE and a maximum of 19.4% and 16.1%, respectively, for NE, and no-effect levels are defined as 80.0%-125.0%. Using the largest estimates of the coefficients of variation, there was at least 80% power for the EE and NE comparisons with 18 subjects. For lemborexant, the estimate of the standard deviation of within-subject differences on the log scale based on a previous lemborexant study (E2006-A001-005; data on file) was 0.238. Based on this estimate, there would be more than 95% power for the lemborexant comparisons with 18 subjects. Assuming a dropout rate of 10%, it was expected that a total of 20 enrolled subjects would be adequate to ensure that 18 subjects completed the study.

To assess potential effects of multiple doses of lemborexant on EE and NE PK, $AUC_{0\text{-t}}$, and C_{max} for EE and $AUC_{0\text{-inf}}$, half-life ($t_{\frac{1}{2}}$), and C_{max} for NE were analyzed using repeated-measures analysis of variance. The log-transformed C_{max}, $AUC_{0\text{-t}}$, $AUC_{0\text{-inf}}$, and $t_{\frac{1}{2}}$ were the dependent variables. Treatment period was treated as a fixed effect and subject as a random effect.

Comparisons were made between period 2, day 15 (test, OC + lemborexant), and period 1, day 1 (reference, OC alone). The results were presented in terms of the ratio of the geometric least squares (LS) means (test/reference) and corresponding 2-sided 90% confidence intervals (CIs). If the 90%CI was within the "no-effect" range of 80.0%-125.0% (per the United States Food and Drug Administration DDI guidance), then no clinically relevant interaction was to be concluded. If the 90%CI was outside the range of 80.0%-125.0%, the clinical relevance of the PK difference was to be further assessed. In addition, t_{max} was analyzed using nonparametric methods.

The effect of a single dose of OC on steady-state PK of lemborexant was evaluated using repeated-measures analysis of variance with log-transformed C_{max}, $AUC_{0\text{-8h}}$, $AUC_{0\text{-24h}}$, and C_{min} as the dependent variables. Comparisons were made between day 14 (reference, lemborexant alone) and day 15 (test, OC + lemborexant). Treatment day was treated as a fixed effect and subject as a random effect. The results were presented in terms of the ratio of the geometric LS means (test/reference) and the corresponding 2-sided 90%CIs. If the 90%CI was within the range of 80.0%-125.0%, then no clinically relevant interaction was to be concluded. In addition, t_{max} was analyzed using nonparametric methods.

Table 1. Demographic Characteristics

Parameter	n = 20
Age (years), mean (SD)	33.6 (6.3)
Fertility status, n (%)	
Childbearing potential	14 (70.0)
Postmenopausal	0
Surgically sterile	6 (30.0)
Race, n (%)	
White	12 (60.0)
Black or African American	8 (40.0)
BMI (kg/m^2), mean (SD)	26.0 (3.2)

BMI, body mass index; SD, standard deviation.

Results

Subject Disposition and Baseline Demographics

Thirty-four subjects were enrolled, and 25 subjects passed screening. Twenty of those subjects (80%) were dosed and completed all assessments. One subject was lost to follow-up, and 4 withdrew consent. Subjects had a mean age of 33.6 years and a mean body mass index of 26.0 kg/m^2. Additional demographic data are reported in Table 1.

Pharmacokinetic Results

The mean plasma concentrations of EE and NE over 96 hours were similar when OC was administered alone (day 1) and when administered with lemborexant at steady state (day 15); see Figures 2-4. The PK parameters (C_{max} and $AUC_{0\text{-inf}}$) of NE were similar

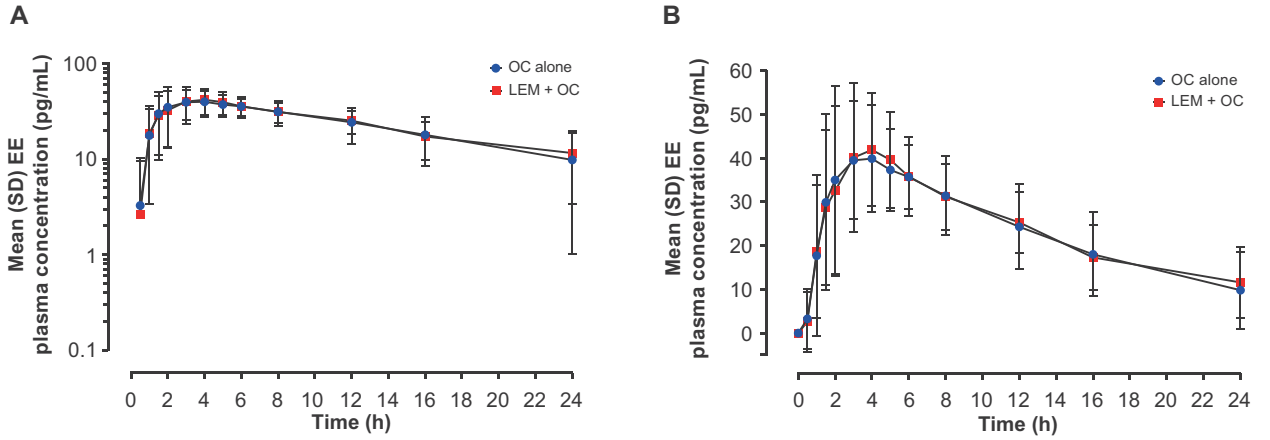

Figure 2. Mean plasma EE concentration-time profiles after administration of a single dose of OC (EE 0.030 mg and NE 1.5 mg; day 1) and coadministration of a single dose of OC (EE 0.030 mg and NE 1.5 mg) with LEM 10 mg once daily (day 15): (A) semi-logarithmic scale and (B) linear scale up to 24 h. EE, ethinyl estradiol; LEM, lemborexant; NE, norethindrone acetate; OC, oral contraceptive; SD, standard deviation.

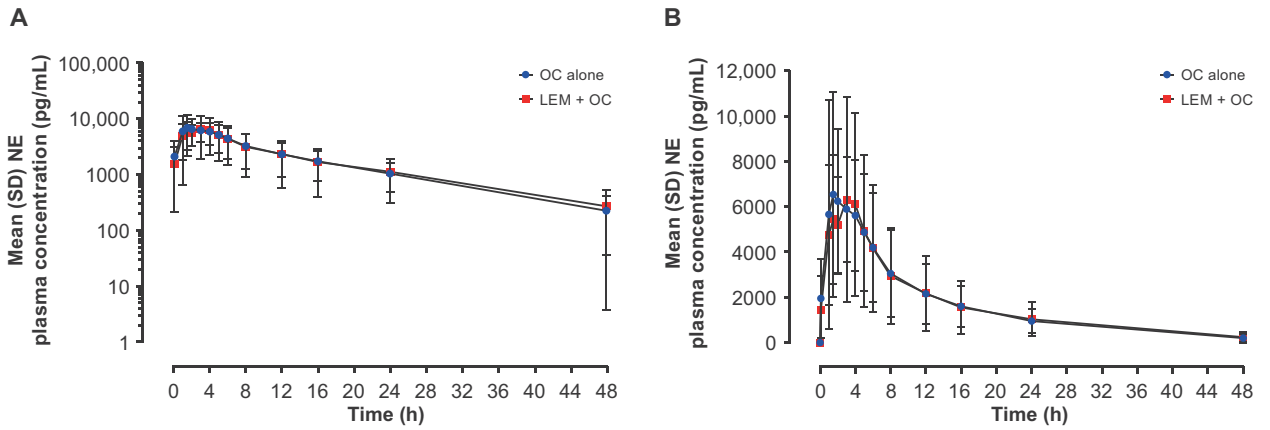

Figure 3. Mean NE concentration-time profiles after administration of a single dose of OC (EE 0.030 mg and NE 1.5 mg; day 1) and coadministration of a single dose of OC (EE 0.030 mg and NE 1.5 mg) with LEM 10 mg once daily (day 15): (A) semi-logarithmic scale and (B) linear scale up to 48 h. EE, ethinyl estradiol; LEM, lemborexant; NE, norethindrone acetate; OC, oral contraceptive; SD, standard deviation.

when OC was administered alone or with lemborexant at steady state. Geometric LS mean ratios for NE parameters ranged from 95.1% to 103.0%, and the 90%CIs were within 80.0%-125.0%. Mean EE C_{max} was similar when OC was administered alone or coadministered with lemborexant at steady state. The geometric LS mean ratio for EE C_{max} was 100.6%, and the 90%CI was within 80.0%-125.0%. The geometric LS mean ratio for EE $AUC_{0\text{-}t}$ was 112.8 with a corresponding 90%CI of 97.1%-131.1%, indicating that the EE $AUC_{0\text{-}t}$ was approximately 13% higher when OC was coadministered with lemborexant (Table 2, Figure 4). This value exceeded the no-effect limit of 80.0%-125.0%.

Although EE $AUC_{0\text{-}inf}$ was in the planned analysis, acceptance criteria (in particular, the requirement for characterizing the terminal rate constant over a time interval at least twice the subsequently estimated terminal $t_{\frac{1}{2}}$ or excluding $AUC_{0\text{-}inf}$ if >20% was determined from extrapolation) were not met in all subjects except 1 subject with OC alone. Therefore, EE $AUC_{0\text{-}inf}$ could not be estimated or reported for most subjects. This parameter was not included in the statistical analysis, and comparisons of overall systemic EE exposure were based on $AUC_{0\text{-}t}$. Only $AUC_{0\text{-}t}$ is presented for EE, whereas $AUC_{0\text{-}inf}$ is presented for NE.

The mean plasma concentrations of lemborexant over 24 hours were similar when lemborexant was administered alone (day 14) and when coadministered with OC (day 15); see Figure 5. Exposure (C_{min}, C_{max}, and AUCs) to lemborexant was similar when lemborexant was administered alone (day 14) and when coadministered with OC (day 15). Geometric mean ratios for lemborexant ranged from 94.0% to 103.6%,

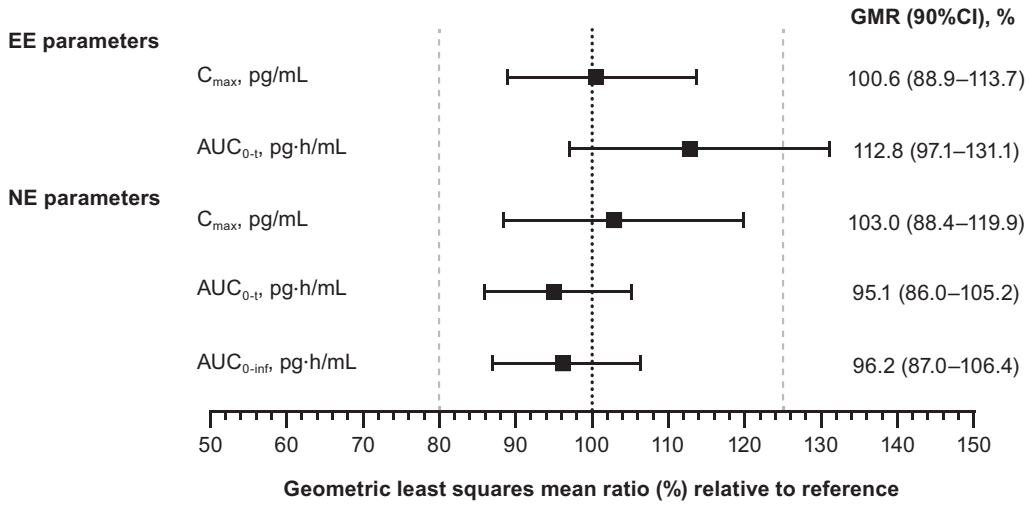

Figure 4. Forest plot of EE and NE exposure after OC alone (EE 0.030 mg and NE 1.5 mg; day 1) and after coadministration of a single dose of OC with lemborexant 10 mg once daily (day 15). Error bars represent 90%CIs. AUC_{0-inf}, area under the plasma concentration-time curve from zero time extrapolated to infinity for NE; AUC_{0-t}, area under the plasma concentration-time curve from zero time to the time of the last quantifiable concentration for EE and NE; C_{max}, maximum plasma drug concentration; CI, confidence interval; EE, ethinyl estradiol; GMR, geometric mean ratio; NE, norethindrone acetate.

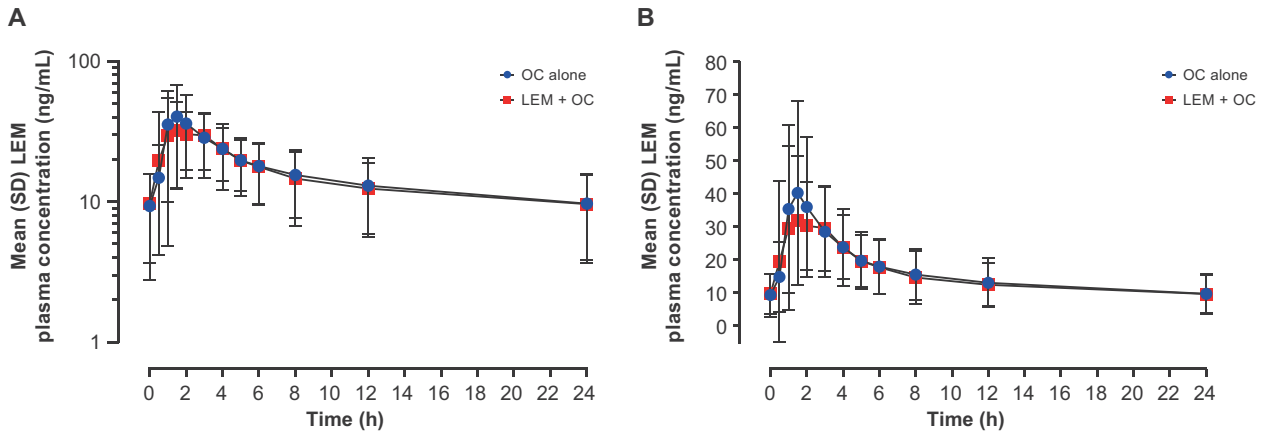

Figure 5. Mean plasma LEM concentration-time profiles after LEM 10 mg once daily (day 14) and after coadministration of a single dose of OC (EE 0.030 mg and NE 1.5 mg) with LEM 10 mg once daily (day 15): (A) semi-logarithmic scale and (B) linear scale up to 24 h. EE, ethinyl estradiol; LEM, lemborexant; NE, norethindrone acetate; OC, oral contraceptive; SD, standard deviation.

and the 90%CIs were within the 80.0%-125.0% limits (Figure 6). Exposure to the metabolites M4, M9, and M10 was also similar when lemborexant was administered alone (day 14) and when coadministered with OC (day 15) (Supplemental Table 1).

Safety

All TEAEs were reported to be mild or moderate, and none resulted in study discontinuation. All reported TEAEs were consistent with the known safety profile of lemborexant.[22,23] No reported TEAEs were considered serious. The most commonly reported TEAEs with lemborexant were dizziness, headache, constipation, and sleep paralysis (Table 3). No subjects withdrew from the study as a result of adverse events.

Discussion

The purpose of this study was to examine the effect of lemborexant on the PK of a single dose of OC, the effect of a single dose of OC on the PK profile of lemborexant at steady state, and the safety of the combination of OC and lemborexant. The impact of lemborexant on EE PK parameters was minimal, and NE PK parameters were not meaningfully impacted. The steady-state lemborexant PK profile was not meaningfully impacted by a single dose of OC. Overall, this study demonstrated that lemborexant and OC can be coadministered in women of childbearing potential without the need for a dose adjustment.

Table 2. Summary of Pharmacokinetic Parameters of EE and NE After Administration of a Single Dose of OC (Day 1) and Coadministration of a Single Dose of OC and LEM (Day 15)

Parameter	Day 1 (OC Alone), n = 20	Day 15 (OC + LEM), n = 20
EE		
t_{max}, h[a]	4.0 (1.5-8.0)	4.0 (1.0-5.0)
C_{max}, pg/mL[b]	47.4 (14.9)	47.7 (15.2)
C_{max}, pg/mL[c]	45.2 (32.4)	45.5 (33.0)
AUC_{0-t}, pg·h/mL[b]	556 (255)	641 (331)
AUC_{0-t}, pg·h/mL[c,d]	507 (46.5)	572 (52.2)
$t_{\frac{1}{2}}$, h[b]	5.7 (NC)	NC
NE		
t_{max}, h[a]	2.0 (1.0-5.0)	3.0 (1.0-6.0)
C_{max}, pg/mL[b]	8520 (3830)	8850 (4280)
C_{max}, pg/mL[c]	7760 (46.8)	7990 (49.1)
AUC_{0-t}, pg·h/mL[b]	76 600 (38 400)	77 200 (50 700)
AUC_{0-t}, pg·h/mL[c]	67 100 (59.3)	63 800 (70.3)
AUC_{0-inf}, pg·h/mL[b]	80 400 (38 200)	84 600 (50 500)
AUC_{0-inf}, pg·h/mL[c]	71 600 (55.1)	72 500 (61.7)
$t_{\frac{1}{2}}$, h[b]	11.1 (3.7)	12.3 (3.6)

AUC_{0-inf}, area under the plasma concentration-time curve from zero time extrapolated to infinity; AUC_{0-t}, area under the plasma concentration-time curve from zero time to time of the last quantifiable concentration; C_{max}, maximum plasma drug concentration; CV, coefficient of variation; EE, ethinyl estradiol; LEM, lemborexant; NC, not calculated; NE, norethindrone acetate; OC, oral contraceptive; t_{max}, time to reach maximum plasma drug concentration.

[a] t_{max} reported as median (range).

[b] C_{max}, AUC_{0-t}, AUC_{0-inf}, and $t_{\frac{1}{2}}$ reported as arithmetic mean (SD).

[c] C_{max}, AUC_{0-t}, and AUC_{0-inf} reported as geometric mean (CV%).

[d] Although EE AUC_{0-inf} was in the planned analysis, acceptance criteria (specifically the requirement for characterizing the terminal rate constant over a time interval at least twice the subsequently estimated terminal half-life or excluding AUC_{0-inf} if >20% was determined from extrapolation) were not met in all subjects except 1 subject with OC alone. Therefore, EE AUC_{0-inf} could not be estimated or reported for most subjects, and this parameter was not included in the statistical analysis; comparisons of overall systemic EE exposure were based on AUC_{0-t}.

Table 3. Summary of Treatment-Emergent Adverse Events

Parameter, n (%)	OC Alone (n = 20)	LEM Alone (n = 20)	OC + LEM (n = 20)
Any TEAE	1 (5.0)	13 (65.0)	5 (25.0)
Any LEM-related TEAE	NA	11 (55.0)	3 (15.0)
Any serious TEAE	0	0	0
AEs in ≥3 subjects (15%) by preferred term, n (%)			
Constipation	0	3 (15.0)	0
Dizziness	0	4 (20.0)	0
Headache	0	4 (20.0)	0
Sleep paralysis	0	3 (15.0)	2 (10.0)

AE, adverse event; LEM, lemborexant; NA, not applicable; OC, oral contraceptive; TEAE, treatment-emergent adverse event.

For EE, C_{max} was not meaningfully impacted by coadministration with lemborexant at steady state, as the 90%CIs were within the no-effect interval of 80.0%-125.0% recommended by the United States Food and Drug Administration DDI guidance for the conduct of in vivo drug interaction studies. The EE AUC_{0-t} showed a 13% increase when coadministered with lemborexant versus with OC alone. However, the upper bound of the 90%CI of the geometric mean ratio slightly exceeded 125.0%. Based on an integrated phase 3 exposure-response analysis that has been established for both safety and efficacy (unpublished data), this small increase in exposure of EE on coadministering lemborexant with OC was not considered clinically relevant. The estrogen component, EE, is typically the most important component in an OC, as it suppresses ovulation, the primary role of an active contraceptive. As coadministration with lemborexant did not decrease EE exposure, this study suggests that lemborexant will not result in a decrease in the effectiveness of a contraceptive when women taking OCs are prescribed lemborexant. In addition, as the C_{max} of EE was contained within the no-effect bounds (lack of increase in EE exposure), this indicates that concomitant administration

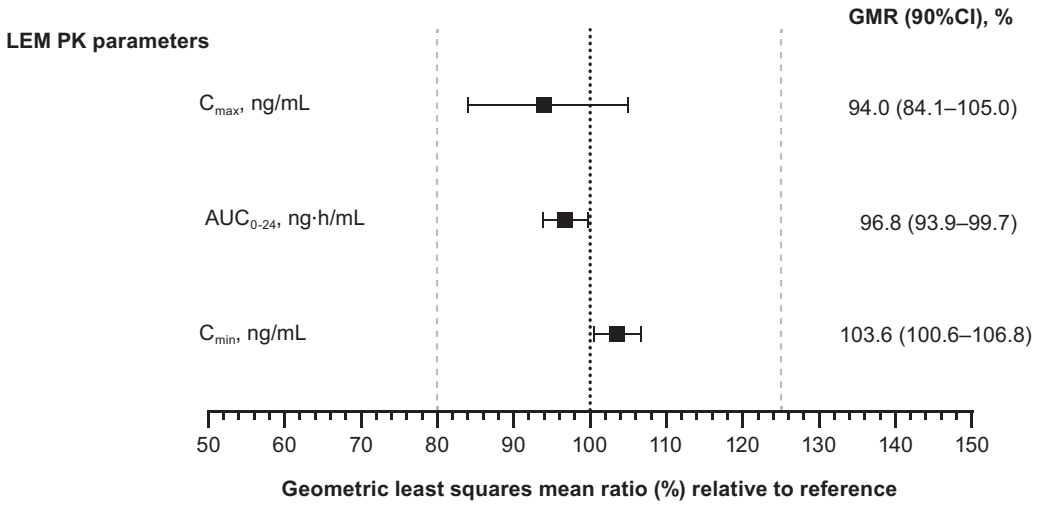

Figure 6. Forest plot of LEM exposure after LEM 10 mg once daily (day 14) and after coadministration of a single dose of OC (ethinyl estradiol 0.030 mg and norethindrone acetate 1.5 mg) with LEM 10 mg once daily (day 15). Error bars represent 90%CIs. AUC_{0-24h}, area under the plasma concentration-time curve from zero time to 24 hours postdose; CI, confidence interval; C_{max}, maximum plasma drug concentration; C_{min}, predose concentration; GMR, geometric mean ratio; LEM, lemborexant; OC, oral contraceptive; PK pharmacokinetics.

of OC with lemborexant is unlikely to cause safety issues related to estrogen overactivity. Furthermore, the small increase in EE AUC_{0-t} suggests no increased risk of vascular thromboembolism.[24]

The NE PK parameters (C_{max} and AUCs) were not meaningfully impacted by coadministration with lemborexant at steady state. The progesterone component 90%CIs were entirely contained within the prespecified no-effect interval of 80.0%-125.0%. Therefore, lemborexant at steady state did not have a clinically meaningful or statistically significant effect on the PK profile of NE.

The mean plasma concentrations and exposure to lemborexant and the metabolites M4, M9, and M10 were similar when lemborexant was administered alone and when coadministered with OC. A single dose of OC did not have a clinically relevant effect on steady-state lemborexant C_{min}, C_{max}, and AUCs.

TEAEs reported during coadministration of lemborexant and OC were mild to moderate. No serious TEAEs were reported. The most common TEAEs in the study were headache, dizziness, sleep paralysis, and constipation. These findings are consistent with the known safety profile of lemborexant. In previous clinical studies of lemborexant, most adverse events were found to be mild to moderate.[1,2,25]

Drug interactions are most likely to occur when patients are on inducers or inhibitors of CYP3A that are coadministered with agents metabolized by CYP3A. Certain medications commonly prescribed for insomnia are also metabolized by CYP3A,[26] increasing the possibility of DDIs with other drugs such as OCs that are similarly metabolized. As lemborexant is not an inducer or a significant inhibitor of CYP3A activity at clinically relevant concentrations, lemborexant is a suitable insomnia treatment for females who are concomitantly prescribed OCs.

Conclusions

In summary, the current study demonstrated that PK parameters for NE stayed within the regulatory limits (90%CI boundary of 80.0%-125.0%), and only minor changes to PK parameters were observed for EE. Mean lemborexant concentrations and PK parameters were similar for lemborexant with OC and lemborexant alone. The coadministration of OC did not have a clinically relevant effect on the steady-state PK profile of lemborexant. TEAEs reported during the study were mild or moderate and consistent with the known lemborexant safety profile. These findings were expected, as there is no mechanism for DDI when lemborexant and OC are coadministered. These results indicate that lemborexant and OC can be coadministered without a dose adjustment.

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Conflicts of Interest

I.L., J.A., N.H., G.F., M.M., and L.R. are employees of Eisai Inc. S.D. is an employee of Eisai Ltd.

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Author Contributions

Study design: I.L., M.M.
Data analyses, interpretation of data, and manuscript preparation: I.L., J.A., N.H., G.F., S.D., M.M., L.R.

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