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

Ishani Landry¹, Jagadeesh Aluri¹, Nancy Hall¹, Gleb Filippov¹, Satish Dayal², Margaret Moline¹, and Larisa Reyderman¹

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

1Eisai Inc., Woodcliff Lake, New Jersey, USA
2Eisai Ltd., Hatfield, UK

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Submitted for publication 5 November 2020; accepted 17 March 2021.

Corresponding Author:
Ishani Landry, PhD, Eisai Inc., 100 Tice Boulevard, Woodcliff Lake, NJ 07677
(e-mail: Ishani_Landry@eisai.com)
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. Although EE has demonstrated a low potential for clinically significant DDIs with several medications, clinically significant interactions have been reported with certain drugs, including ritonavir, carbamazepine, phenytoin, phenobarbital, and rifampicin. 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.

EE is metabolized mainly through sulfation and hydroxylation by CYP3A13 and glucuronidation. NE is primarily metabolized by CYP3A, sulftotransferases, and uridine 5-diphospho-glucuronosyltransferase. Lemborexant is also primarily metabolized by CYP3A, as shown by in vitro studies. 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. 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. 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. The key metabolites of lemborexant are M4, M9, and M10 (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. 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.

**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.

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 validated by analyzing 6 replicate quality controls at 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 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 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 291.0 → 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$_1$, 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$_{0-24h}$), 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$_{0-1}$),
AUC from zero time extrapolated to infinity (AUC$_{0\text{-inf}}$), C$_{\text{max}}$, and t$_{\text{max}}$ 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$_{\text{max}}$) and log (AUC$_{\text{tau}}$), 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$_{\text{max}}$ for NE were analyzed using repeated-measures analysis of variance with log-transformed C$_{\text{max}}$, AUC$_{0\text{-8h}}$, AUC$_{0\text{-24h}}$, and C$_{\text{min}}$ as the dependent variables. Comparisons were made between period 2, day 15 (test, OC + lemborexant) and period 1, day 1 (reference, OC alone). 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% 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$_{\text{max}}$ 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$_{\text{max}}$, AUC$_{0\text{-8h}}$, AUC$_{0\text{-24h}}$, and C$_{\text{min}}$ 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$_{\text{max}}$ was analyzed using nonparametric methods.

**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$_{\text{max}}$ and AUC$_{0\text{-inf}}$) of NE were similar

| 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.
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 $C_{\text{max}}$ was similar when OC was administered alone or coadministered with lemborexant at steady state. The geometric LS mean ratio for EE $C_{\text{max}}$ was 100.6%, and the 90% CI was within 80.0%-125.0%. The geometric LS mean ratio for EE AUC$_{0-t}$ was 112.8 with a corresponding 90% CI of 97.1%-131.1%, indicating that the EE AUC$_{0-t}$ 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 $t_1$ 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$_{0-t}$. Only AUC$_{0-t}$ 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 ($C_{\text{min}}$, $C_{\text{max}}$, 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<sub>0-∞</sub>, area under the plasma concentration-time curve from zero time extrapolated to infinity for NE; AUC<sub>0-t</sub>, area under the plasma concentration-time curve from zero time to the time of the last quantifiable concentration for EE and NE; C<sub>max</sub>, maximum plasma drug concentration; Cl, 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        |                          |                           |
| \( t_{\text{max}} \), h \(^a\) | 4.0 (1.5-8.0) | 4.0 (1.0-5.0) |
| \( C_{\text{max}} \), pg/mL \(^b\) | 47.4 (14.9) | 47.7 (15.2) |
| \( C_{\text{max}} \), pg/mL \(^c\) | 45.2 (32.4) | 45.5 (33.0) |
| \( \text{AUC}_{0-t} \), pg·h/mL \(^b\) | 556 (255) | 641 (331) |
| \( \text{AUC}_{0-t} \), pg·h/mL \(^d\) | 507 (46.5) | 572 (52.2) |
| \( t_{\frac{1}{2}} \), h \(^e\) | 5.7 (HC) | NC |
| NE        |                          |                           |
| \( t_{\text{max}} \), h \(^a\) | 2.0 (1.0-5.0) | 3.0 (1.0-6.0) |
| \( C_{\text{max}} \), pg/mL \(^b\) | 8520 (3830) | 8850 (4280) |
| \( C_{\text{max}} \), pg/mL \(^c\) | 7760 (46.8) | 7990 (49.1) |
| \( \text{AUC}_{0-t} \), pg·h/mL \(^b\) | 76 600 (38 400) | 77 200 (50 700) |
| \( \text{AUC}_{0-t} \), pg·h/mL \(^d\) | 67 100 (59.3) | 63 800 (70.3) |
| \( \text{AUC}_{0-t} \), pg·h/mL \(^c\) | 80 400 (38 200) | 84 600 (50 500) |
| \( t_{\frac{1}{2}} \), h \(^e\) | 71 600 (55.1) | 72 500 (61.7) |
| \( t_{\frac{1}{2}} \), h \(^e\) | 1.1 (3.7) | 12.3 (3.6) |

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

\(^a\) \( t_{\text{max}} \) reported as median (range).

\(^b\) \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-t} \), and \( t_{\frac{1}{2}} \) reported as arithmetic mean (SD).

\(^c\) \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-t} \) reported as geometric mean (CV%).

\(^d\) Although EE \( \text{AUC}_{0-t} \) 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 \( \text{AUC}_{0-t} \) if \( > 20\% \) was determined from extrapolation) were not met in all subjects except 1 subject with OC alone. Therefore, EE \( \text{AUC}_{0-t} \) 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 \( \text{AUC}_{0-t} \).

Table 3. Summary of Treatment-Emergent Adverse Events

| Parameter | 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, \( C_{\text{max}} \) 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 \( \text{AUC}_{0-t} \) 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 \( C_{\text{max}} \) of EE was contained within the no-effect bounds (lack of increase in EE exposure), this indicates that concomitant administration
of OC with lemborexant is unlikely to cause safety issues related to estrogen overactivity. Furthermore, the small increase in EE AUC suggests no increased risk of vascular thromboembolism.

The NE PK parameters (C\text{max} and AUCs) were not meaningfully impacted by coadministration with lemborexant at steady state. The progesterone component 90%CIs were entirely contained within the pre-specified 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\text{min}, C\text{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.\textsuperscript{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, 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.

Acknowledgments

Manuscript development assistance was provided by Jim Ferry, PhD, of Eisai Inc. Medical writing assistance was provided by Maureen Wallace, PhD, of ProScribe – Envision Pharma Group and was funded by Eisai Inc.
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.

Funding
This research was supported by Eisai Inc. The investigators retained full independence in the conduct of this research.

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.

References
1. Murphy P, Moline M, Mayleben D, et al. Lemborexant, a dual orexin receptor antagonist (DORA) for the treatment of insomnia disorder: results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. J Clin Sleep Med. 2017;13(11):1289-1299.
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 Network Open. 2019;2(12):e1918254.
3. Kärppä M, Yardley J, Pinner K, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: a phase 3 randomized clinical trial. JAMA Network Open. 2019;2(12):e1918254.
4. Ouellet D, Hsu A, Qian J, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. Br J Clin Pharmacol. 1998;46(2):111-116.
5. Nelson AL, Cohen S, Galitsky A, et al. Women’s perceptions and treatment, patterns related to contraception: results of a survey of US women. Contraception. 2018;97(3):256-263.
6. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2014;6:1-13.
7. Xu Y, Gabriel K, Wang Y, et al. A multi-center, open-label, pharmacokinetic drug interaction study of erenumab and a combined oral contraceptive in healthy females. CNS Drugs. 2019;33(5):513-522.
8. Zhang H, Cui D, Wang B, et al. Pharmacokinetic drug interactions involving 17α-ethinylestradiol. Clin Pharmacokinet. 2007;46(2):133-157.
9. Butler K, Teng R. Effect of ticagrelor on the pharmacokinetics of ethinyl oestradiol and levonorgestrel in healthy volunteers. Curr Med Res Opin. 2011;27(8):1585-1593.
10. Friedrich C, Port A, Ring A, et al. Effect of multiple oral doses of linagliptin on the steady-state pharmacokinetics of a combination oral contraceptive in healthy female adults: an open-label, two-period, fixed-sequence, multiple-dose study. Clin Drug Investig. 2011;31(9):643-653.
11. Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010;3(2):183-192.
12. Bolt HM, Bolt M, Kappus H. Interaction of rifampicin treatment with pharmacokinetics and metabolism of ethinylestradiol in man. Acta Endocrinol. 1977;85(1):189-197.
13. Landry I, Aluri J, Nakai K, et al. Evaluation of the CYP3A and CYP2B6 drug-drug interaction potential of lemborexant. Clin Pharmacol Drug Dev. 2021; doi.org/10.1002/cpdd.915.
14. Wang B, Sanchez RI, Franklin RB, Evans DC, Huskey SE. The involvement of CYP3A4 and CYP2C9 in the metabolism of 17α-ethinylestradiol. Drug Metab Dispos. 2004;32(11):1209-1212.
15. Zhang N, Shon J, Kim MJ, et al. Role of CYP3A in oral contraceptives clearance. Clin Transl Sci. 2018;11(3):251-260.
16. Ueno T, Rege B, Aluri J, Kusano K. Effect of itraconazole on PK profile of lemborexant in healthy volunteers and application of PBPK modeling to DDI simulations with CYP3A inhibitor. Drug Metab Pharmacokinet. 2017;33(Suppl):S46.
17. Landry I, Nakai K, Ferry J, et al. Pharmacokinetics, pharmacodynamics, and safety of the dual orexin receptor antagonist lemborexant: findings from single-dose and multiple-ascending-dose phase I studies in healthy adults. Clin Pharmacol Drug Dev. 2021;10(2):153-165.
18. Wilkinson GR. Cytochrome P450A (CYP3A) metabolism: prediction of In Vivo activity in humans. J Pharmacokinet Biopharm. 1996;24(5):475-490.
19. Pastino G, Hall N, Aluri J, et al. Effects of lemborexant, a dual orexin receptor antagonist, on CYP3A and CYP2B6 activity in healthy volunteers. Clin Pharmacol Drug Dev. 2015;4(Suppl 1):7.
20. Mano Y, Ueno T, Hotta K. Establishment of a simultaneous assay for lemborexant, a novel dual orexin receptor antagonist, and its three metabolites, and its application to a clinical protein binding study. J Pharm Biomed Anal. 2020;187:113359.
21. Ueno T, Ishida T, Aluri J, et al. Disposition and metabolism of [14C]lemborexant in healthy human subjects and characterization of its circulating metabolites. Drug Metab Dispos. 2021;49(1):31-38.
22. Hoyer D, Jacobson LH. Lemborexant dual orexin receptor antagonist treatment of insomnia. Drug Fut. 2018;43(10):715-730.
23. 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(4):9.
24. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ*. 2019;364:k4810.

25. Murphy P, Kumar D, Zammit G, Rosenberg R, Moline M. Safety of lemborexant versus placebo and zolpidem: effects on auditory awakening threshold, postural stability, and cognitive performance in healthy older subjects in the middle of the night and upon morning awakening. *J Clin Sleep Med*. 2020;16(5):765-773.

26. Greenblatt DJ, Zammit GK. Pharmacokinetic evaluation of eszopiclone: clinical and therapeutic implications. *Expert Opin Drug Metab Toxicol*. 2012;8(12):1609-1618.

**Supplemental Information**

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.