

# Evaluation of the CYP3A and CYP2B6 Drug-Drug Interaction Potential of Lemborexant

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## Abstract

Lemborexant is approved for treating insomnia and is under investigation for treating irregular sleep-wake rhythm disorder. Based on in vitro drug-drug interaction (DDI) characteristics, phase I, open-label DDI studies were conducted to evaluate lemborexant's cytochrome P450 3A (CYP3A) and CYP2B6 interaction potential. Interactions between lemborexant 10 mg and strong and moderate CYP3A inhibitors (itraconazole and fluconazole), a strong CYP3A inducer (rifampin), and CYP3A (midazolam) and CYP2B6 substrates (bupropion) were evaluated. Coadministration of lemborexant with itraconazole or fluconazole resulted in 1.4- to 1.6-fold and 3.7- to 4-fold increases in lemborexant maximum observed concentration ( $C_{max}$ ) and area under the concentration-time curve from zero time extrapolated to infinity ( $AUC_{0-inf}$ ), respectively. Coadministration of lemborexant with rifampin resulted in >90% decreases in lemborexant  $C_{max}$  and  $AUC_{0-inf}$ . Midazolam exposure was not affected. Coadministration of lemborexant with bupropion resulted in 49.9% and 45.5% decreases in S-bupropion  $C_{max}$  and  $AUC_{0-inf}$ , respectively. Comparison of estimated exposures for patients in phase 3 trials who were/were not receiving concomitant weak CYP3A inhibitors substantiated the DDI pharmacokinetic findings. Lemborexant was generally well tolerated in the phase I studies. In summary, lemborexant does not affect the pharmacokinetics of CYP3A substrates and has potential to induce CYP2B6. Consistent with in vitro findings, moderate and strong CYP3A inhibitors and inducers affected the pharmacokinetics of lemborexant; hence, patients taking lemborexant 5 or 10 mg should avoid coadministration with moderate and strong CYP3A inhibitors and inducers.

## Keywords

CYP2B6, CYP3A, drug-drug interaction, lemborexant, orexin receptor antagonists, pharmacokinetics

Lemborexant (also referred to as E2006 and Dayvigo<sup>TM</sup>), a dual orexin receptor antagonist,<sup>1</sup> was recently approved by the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency for the treatment of insomnia in adults and is currently under investigation for the treatment of irregular sleep-wake rhythm disorder. Findings from 2 pivotal phase 3 clinical studies of lemborexant in subjects with insomnia (study E2006-G000-304 [study 304; SUNRISE-1; NCT02783729] and study E2006-G000-303 [study 303; SUNRISE-2; NCT02952820]) demonstrated that lemborexant 5 and 10 mg significantly improved sleep onset and maintenance compared with placebo.<sup>2,3</sup> Lemborexant was well tolerated in both phase 3 studies.<sup>2,3</sup>

Patients with insomnia, in particular, the elderly, may take medications to treat comorbid conditions. Therefore, given the likelihood of polypharmacy among

patients with insomnia, evaluating the drug-drug interaction (DDI) potential of lemborexant is of clear importance. In vitro metabolism studies demonstrated

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that lemborexant is predominantly metabolized by the cytochrome P450 3A (CYP3A) pathway (unpublished data). Lemborexant has 3 main metabolites (all substrates of P-glycoprotein [P-gp]); M4, M9, and M10, of which M10 is the only major circulating metabolite. As previously noted,<sup>4</sup> findings from nonclinical studies have shown that M10 contributes little to the pharmacologic activity of lemborexant (because of the lack of blood-brain barrier penetration<sup>5</sup>) and is not clinically important. In vitro DDI assessments showed that lemborexant and M10 show time-dependent inhibition on CYP3A (61.5% and 34.7% inhibition, respectively, at 30  $\mu\text{mol/L}$ ; unpublished data) and have the potential to induce CYP2B6 and CYP3A, but do not inhibit other CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2A6, CYP2C19, and CYP2E1) or transporters (P-gp, breast cancer resistance protein, bile salt export pump, organic anion transporter [OAT] 1, OAT3, OAT polypeptide [OATP] 1B1, OATP1B3, organic cation transporter 1 [OCT1], OCT2, multidrug and toxic extrusion transporter [MATE] 1, and MATE2-K). Further evaluations determined kinetic parameters for time-dependent inhibition by lemborexant on CYP3A (a maximal inactivation rate constant [ $k_{\text{inact}}$ ] of 0.0503/min and a half-maximal inhibitory concentration of the maximal inactivation rate constant [ $K_{\text{i}}$ ] of 25.2  $\mu\text{mol/L}$ ; unpublished data), suggesting a potential DDI caused by intestinal CYP3A inhibition after oral dosing of lemborexant. Lemborexant was also found to be a potential poor substrate of P-gp, whereas M10 was found to be a substrate of P-gp. Finally, in vitro studies revealed that neither lemborexant nor M10 was a substrate of BCRP, OATP1B1, or OATP1B3.

The aim of the analyses reported here was to evaluate the CYP3A and CYP2B6 DDI potential of lemborexant using data from 2 phase 1 studies. Per US Food and Drug Administration guidance, the choice of drugs evaluated in the phase 1 studies included itraconazole and fluconazole (strong and moderate CYP3A inhibitors, respectively), rifampin (strong CYP3A inducer), midazolam (CYP3A substrate), and bupropion (CYP2B6 substrate).

## Methods

Study protocols were approved by an institutional review board at each study site, and the studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and all applicable local regulations. All subjects provided written informed consent. The studies were carried out at single sites: PPD Development LLC (Austin, Texas; study E2006-A001-004 [study 004; NCT02085967]) or Worldwide Clini-

cal Trials (San Antonio, Texas; E2006-A001-012 [study 012; NCT03451110]).

## Phase 1 Studies

The DDI potential of lemborexant was evaluated in 2 phase 1 open-label studies (studies 004 and 012).

*Lemborexant, Itraconazole (Strong CYP3A Inhibitor), Rifampin (Strong CYP3A Inducer), Midazolam (CYP3A Substrate), and Bupropion (CYP2B6 Substrate) Interaction Study.* Interactions between lemborexant and itraconazole, rifampin, midazolam, and bupropion were each examined in a 2-part phase 1 open-label study (study 004).

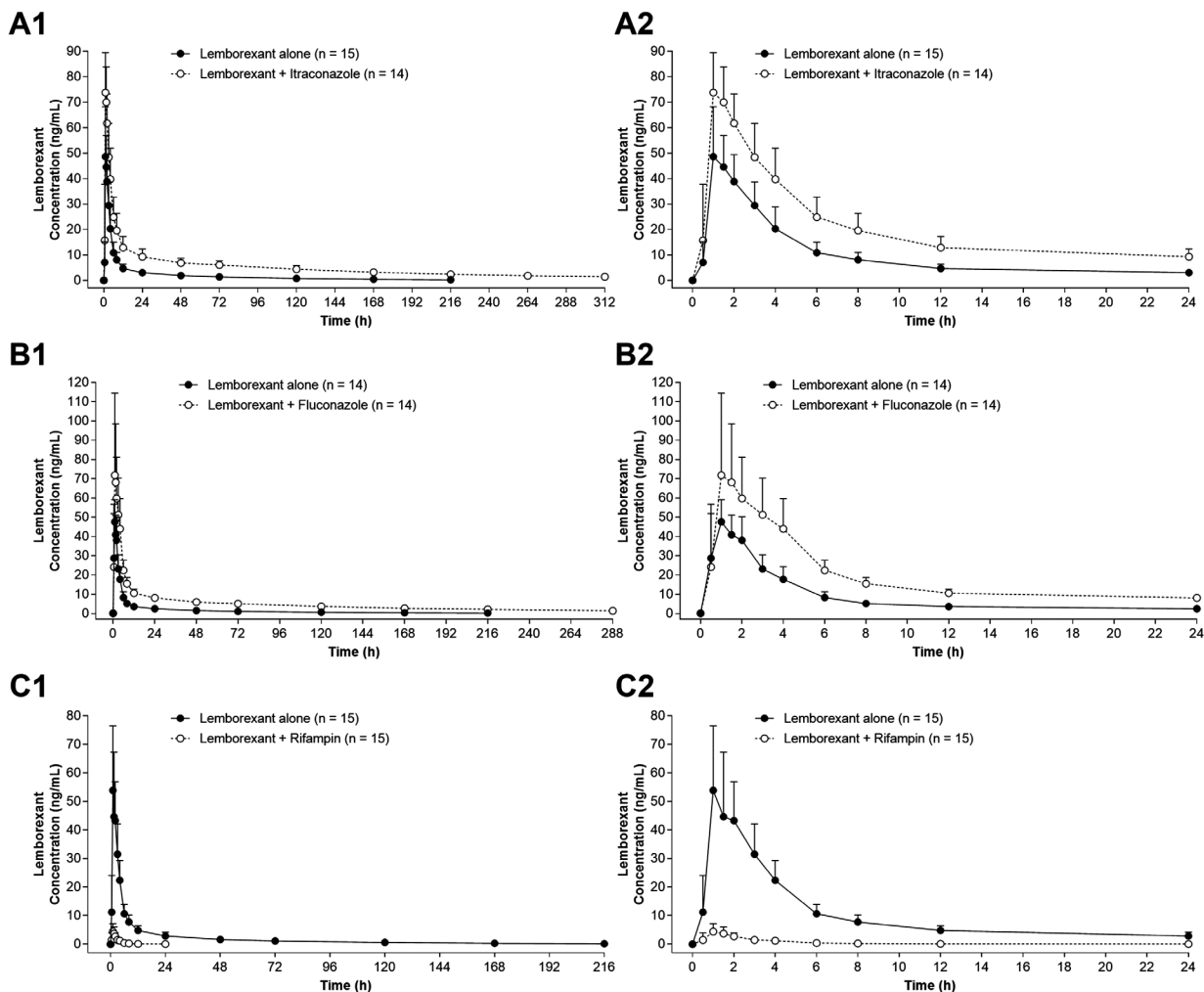
In part A (lemborexant as DDI victim), healthy adult subjects received a single dose of lemborexant 10 mg on day 1, itraconazole 200 mg once daily for 20 days (days 15-34), and a single dose of lemborexant 10 mg on day 22. An additional cohort of healthy adult subjects received a single dose of lemborexant 10 mg on day 1, rifampin 600 mg once daily for 20 days (days 15-34), and a single dose of lemborexant 10 mg on day 22. Study drug was administered in the morning, and blood samples for pharmacokinetic (PK) analysis were collected predose and for up to 216 hours after lemborexant administration on day 1 and predose and for up to 312 hours after lemborexant + itraconazole or rifampin administration on day 22.

In part B (lemborexant as DDI perpetrator), healthy adult subjects received midazolam 2 mg + bupropion 75 mg on day 1, lemborexant 10 mg for 13 days (days 8-20), and midazolam 2 mg + bupropion 75 mg on day 17. Study drug was administered in the morning, and blood samples for PK analysis were collected predose and for up to 96 hours after treatment administration on days 1 and 17.

*Lemborexant and Fluconazole (Moderate CYP3A Inhibitor) Interaction Study.* Interactions between lemborexant and fluconazole were examined in a phase 1 open-label study (study 012).

Healthy adult subjects received a single dose of lemborexant 10 mg on day 1, underwent a washout period until day 11, received fluconazole once daily for 16 days (400 mg starting on day 11 and 200 mg on days 12-26), and a single dose of lemborexant on day 15. Study drug was administered in the morning, and blood samples for PK analysis were collected predose and up to 216 hours after treatment administration on days 1 and 15.

*PK Assessments.* In both phase 1 studies, plasma concentrations of lemborexant were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.<sup>4</sup> The internal standard was deuterated lemborexant. Chromatographic separation was achieved using a HyperClone (Phenomenex, Torrance, California), 3  $\mu\text{m}$  DBS, C18,



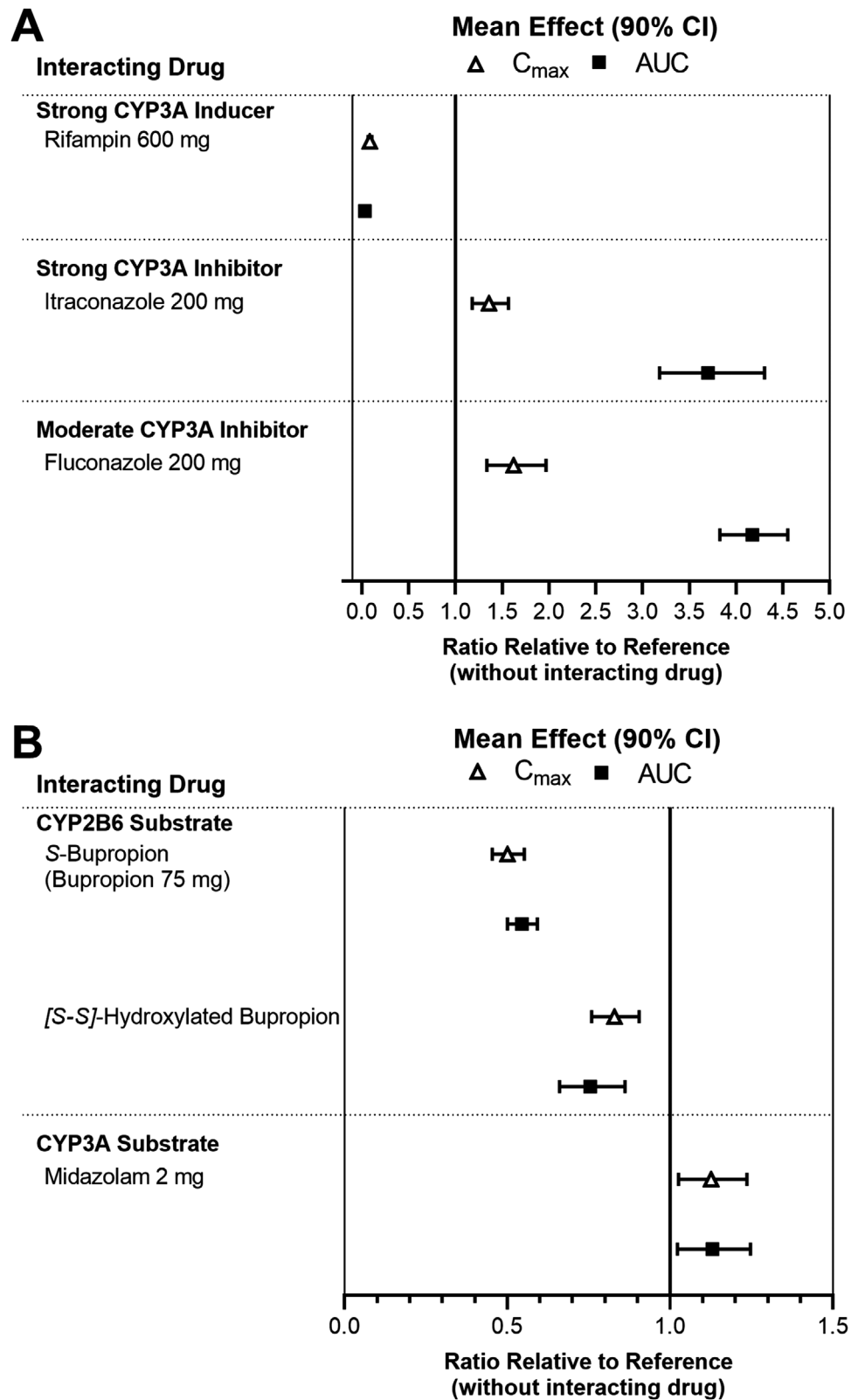
**Figure 1.** Plasma lemborexant concentration-time profiles after single-dose lemborexant 10 mg alone and lemborexant 10 mg + itraconazole 200 mg (A1, A2), fluconazole 200 mg (B1, B2), or rifampin 600 mg (C1, C2). Data are mean (standard deviation).

LC-MS column, 50 × 2 mm with a gradient mobile phase. The mass spectrometer, SCIEX API-5500 (SCIEX, Redwood City, California), was operated in positive electrospray ionization mode with the multiple reaction monitoring of the precursor-to-product ion pairs for lemborexant ( $m/z$  411.0 → 287.1) and deuterated lemborexant ( $m/z$  414.1 → 290.1). Samples were quantified using peak area ratios. The interday precision (coefficient of variation) was ≤7.0%, and accuracy was within 6.5% of nominal. Intraday precision (coefficient of variation) was ≤10.4%, and accuracy was within 9.8% of the nominal. The lower limit of quantitation was 0.10 ng/mL. The calibration curve ranged from 0.100 to 100 ng/mL. Noncompartmental PK parameters assessed from plasma concentration-time data included maximum observed concentration ( $C_{max}$ ), area under the concentration-time curve from zero time to time of last measurable concentration ( $AUC_{0-t}$ ), and AUC from zero time extrapolated to infinity ( $AUC_{0-inf}$ ). Analyses were performed using

Phoenix WinNonlin, version ≥6.2 (Certara, L.P., Princeton, New Jersey).

Midazolam in human plasma containing sodium heparin as anticoagulant was determined using a validated LC-MS/MS method. The analyte, along with deuterated internal standard, was isolated through liquid-liquid extraction from 200- $\mu$ L aliquots of plasma. The organic layer was evaporated under a nitrogen stream and reconstituted for analysis using a Varian Pursuit XRs 5 C18, 50 × 2 mm, 5  $\mu$ m, high-performance liquid chromatography (HPLC) column (Agilent Technologies, Inc., Santa Clara, California) with MS/MS detection using a SCIEX API 4000 in positive ion electrospray mode. Midazolam and its deuterated internal standard were monitored using the mass transitions  $m/z$  326.1 → 291.2 and  $m/z$  332.0 → 295.2, respectively. The nominal range of the assay was 0.100–100 ng/mL in human plasma.

S-bupropion and [*S,S*]-hydroxylated bupropion in human plasma containing dipotassium



**Figure 2.** Forest plot summarizing the effect of coadministered drugs on lemborexant pharmacokinetics (A) and the effect of lemborexant on the pharmacokinetics of coadministered drugs (B). AUC, area under the concentration-time curve; CI, confidence interval;  $C_{max}$ , maximum observed concentration; CYP, cytochrome P450.

**Table 1.** Lemborexant PK Parameters After Single-Dose Administration When Coadministered With Itraconazole, Rifampin, or Fluconazole

Lemborexant 10 mg + Itraconazole 200 mg			
PK Parameter	Lemborexant (n = 15)	Lemborexant + Itraconazole (n = 15)	Geometric Mean Ratio (90%CI)
AUC <sub>0-t</sub> , ng·h/mL			
Geometric LSM	411	1480 <sup>a</sup>	3.605 (3.122-4.162)
Mean (SD)	437 (154)	1540 (374)	—
AUC <sub>0-inf</sub> , ng·h/mL			
Geometric LSM	433	1600 <sup>b</sup>	3.702 (3.183-4.306)
Mean (SD)	464 (175)	1640 (422)	—
C <sub>max</sub> , ng/mL			
Geometric LSM	54.3	73.9 <sup>a</sup>	1.360 (1.181-1.567)
Mean (SD)	55.9 (14.3)	75.0 (12.9)	—
t <sub>1/2</sub> , h			
Mean (SD)	54.4 (13.9)	118 (37.0)	—
Lemborexant 10 mg + Rifampin 600 mg			
PK Parameter	Lemborexant (n = 15)	Lemborexant + Rifampin (n = 15)	Geometric Mean Ratio (90%CI)
AUC <sub>0-t</sub> , ng·h/mL			
Geometric LSM	374	12.3	0.033 (0.027-0.040)
Mean (SD)	409 (178)	13.5 (6.1)	—
AUC <sub>0-inf</sub> , ng·h/mL			
Geometric LSM	389	13.4 <sup>c</sup>	0.034 (0.026-0.045)
Mean (SD)	428 (195)	15.8 (7.7)	—
C <sub>max</sub> , ng/mL			
Geometric LSM	55.5	4.7	0.085 (0.067-0.107)
Mean (SD)	58.9 (21.0)	5.3 (2.6)	—
t <sub>1/2</sub> , h			
Mean (SD)	45.6 (21.2)	10.8 (7.1)	—
Lemborexant 10 mg + Fluconazole 200 mg			
PK Parameter	Lemborexant (n = 14)	Lemborexant + Fluconazole (n = 14)	Geometric Mean Ratio (90%CI)
AUC <sub>0-t</sub> , ng·h/mL			
Geometric LSM	354	1330	3.759 (3.486-4.053)
Mean (SD)	366 (92.6)	1360 (294)	—
AUC <sub>0-inf</sub> , ng·h/mL			
Geometric LSM	374	1560 <sup>d</sup>	4.175 (3.828-4.553)
Mean (SD)	390 (113)	1540 (439)	—
C <sub>max</sub> , ng/mL			
Geometric LSM	54.4	88.3	1.622 (1.336-1.969)
Mean (SD)	56.2 (14.5)	92.8 (27.8)	—
t <sub>1/2</sub> , h			
Mean (SD)	55.4 (21.2)	99.5 (25.7)	—

AUC<sub>0-inf</sub>, area under the concentration-time curve from zero time extrapolated to infinity; AUC<sub>0-t</sub>, area under the concentration-time curve from zero time to time of last measurable concentration; CI, confidence interval; C<sub>max</sub>, maximum observed concentration; LSM, least-squares mean; PK, pharmacokinetic; SD, standard deviation; t<sub>1/2</sub>, half-life.

<sup>a</sup>n = 14.

<sup>b</sup>n = 11.

<sup>c</sup>n = 9.

<sup>d</sup>n = 12.

ethylenediaminetetraacetic acid ( $K_2$ -EDTA) as anticoagulant was determined using a validated LC-MS/MS method. The method used a phospholipid removal plate to extract the analytes from 50- $\mu$ L aliquots of plasma containing  $K_2$ -EDTA along with deuterated internal standards. The final extract was diluted and analyzed using a CHIRALPAK AGP,  $2 \times 100$  mm, 5  $\mu$ m, HPLC column (Sigma-Aldrich, St Louis, Missouri) with MS/MS detection using a SCIEX API 5000 in positive ion electrospray mode. *S*-bupropion and its deuterated internal standard were monitored using the mass transitions  $m/z$  240.1  $\rightarrow$  184.0 and  $m/z$  249.3  $\rightarrow$  185.0, respectively. [*S,S*]-Hydroxylated bupropion and its deuterated internal standard were monitored using the mass transitions  $m/z$  256.2  $\rightarrow$  139.0 and  $m/z$  262.2  $\rightarrow$  244.2, respectively. The nominal ranges for *S*-bupropion and [*S,S*]-hydroxylated bupropion in plasma were 0.500-200 and 2.50-1000 ng/mL, respectively. Plasma concentrations of *S*-bupropion and [*S,S*]-hydroxylated bupropion, rather than racemic hydroxylated bupropion, were evaluated as these metabolites provide a relevant indication of CYP2B6 activity.<sup>6</sup>

When calculating the mean concentration at a given time, all values below the limit of quantification were assigned a value of zero.

**Safety Assessments.** In both phase 1 studies, safety assessments comprised monitoring and recording all treatment-emergent adverse events (AEs) and serious AEs; monitoring of serum chemistry, hematology, and urinalysis values; periodic measurement of vital signs and electrocardiograms; and physical examinations. As lemborexant is expected to cause sleepiness, somnolence was not reported as a treatment-emergent AE if the event occurred between 15 minutes and 9 hours postdose (unless the investigator decided that the event was more pronounced than was expected). AEs were coded per Medical Dictionary for Regulatory Activities, version  $\geq 16.1$ .

**Statistical Analysis.** Treatment effects were assessed using linear mixed-effects models and considered the natural-log-transformed PK parameters were fitted with treatment as a fixed effect and subject as a random effect. Geometric least-squares means and geometric least-squares mean ratios were back-transformed from least-squares means and treatment mean differences. Results are presented as the ratio of the geometric least-squares means (test/reference) and corresponding 2-sided 90% confidence interval.

## Results

### Disposition and Demographics

**Lemborexant, itraconazole, rifampin, midazolam, and bupropion interaction study.** Fifty-eight subjects passed screening; all were dosed and completed the study (part A,

$n = 30$ ; part B,  $n = 28$ ). Demographics of subjects in part A included: a mean  $\pm$  standard deviation (SD) age of  $33.5 \pm 10.3$  years; 27 men (90.0%) and 3 women (10.0%); and a mean  $\pm$  SD body mass index of  $26.9 \pm 3.5$  kg/m<sup>2</sup>. Demographics of subjects in part B included a mean  $\pm$  SD age of  $35.6 \pm 9.9$  years; 24 men (85.7%) and 4 women (14.3%); and a mean  $\pm$  SD body mass index of  $26.0 \pm 3.1$  kg/m<sup>2</sup>.

**Lemborexant and fluconazole interaction study.** Twenty subjects passed screening; of these, 14 were dosed and completed the study. Demographics of subjects included a mean  $\pm$  SD age of  $37.4 \pm 10.4$  years; 6 men (42.9%) and 8 women (57.1%); and a mean  $\pm$  SD body mass index of  $25.8 \pm 3.0$  kg/m<sup>2</sup>.

### Lemborexant Interaction Findings

**Itraconazole (Strong CYP3A Inhibitor).** Plasma lemborexant concentrations with and without itraconazole are shown in Figure 1A. Coadministration of lemborexant with itraconazole resulted in 1.4-fold and 3.7-fold increases in lemborexant  $C_{max}$  and  $AUC_{0-inf}$ , respectively (Figure 2A, Table 1).

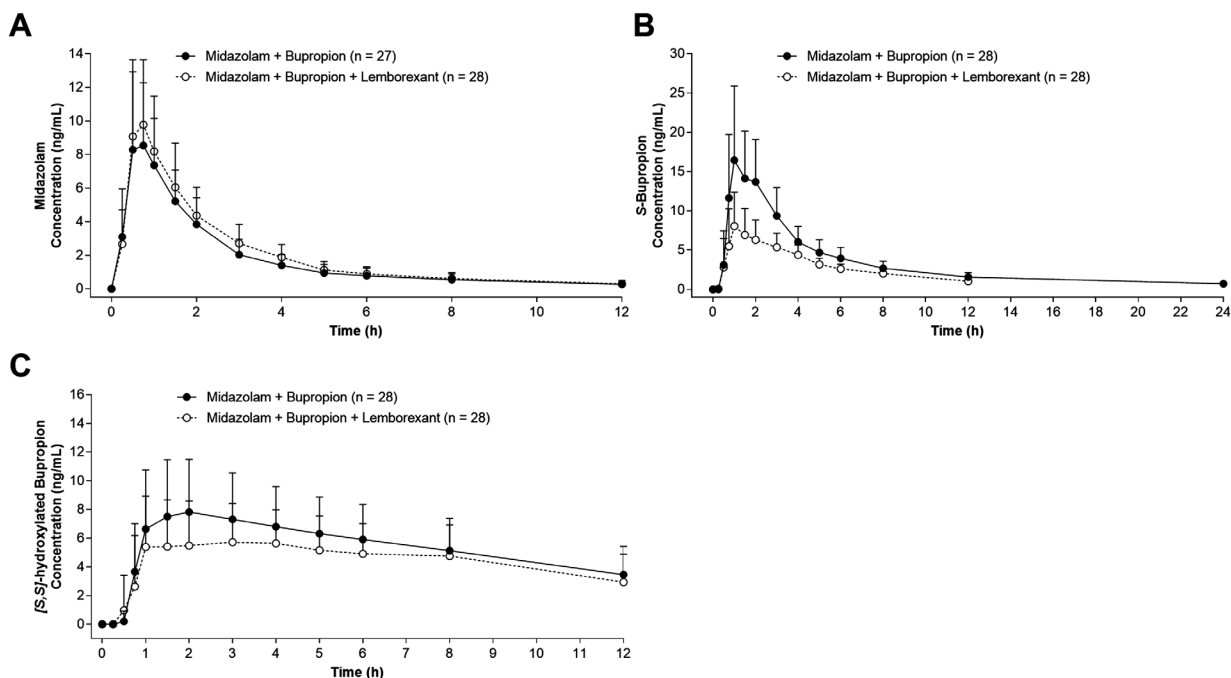
**Fluconazole (Moderate CYP3A Inhibitor).** Plasma lemborexant concentrations with and without fluconazole are shown in Figure 1B. Coadministration of lemborexant with fluconazole resulted in a 1.6-fold increase in lemborexant  $C_{max}$  and an approximate 4-fold increase in lemborexant  $AUC_{0-inf}$  (Figure 2A, Table 1).

**Rifampin (Strong CYP3A Inducer).** Plasma lemborexant concentrations with and without rifampin are shown in Figure 1C. Coadministration of lemborexant with rifampin resulted in  $>90\%$  decreases in lemborexant  $C_{max}$  and  $AUC_{0-inf}$  (Figure 2A, Table 1).

**Midazolam (CYP3A Substrate).** Plasma midazolam concentrations with and without lemborexant are shown in Figure 3A. Midazolam exposure was not affected by coadministration with lemborexant (Figure 2B, Table 2).

**Bupropion (CYP2B6 Substrate).** Plasma *S*-bupropion and [*S,S*]-hydroxylated bupropion concentrations with and without lemborexant are shown in Figure 3B,C, respectively. Coadministration of lemborexant with bupropion resulted in 49.9% and 45.5% decreases in *S*-bupropion  $C_{max}$  and  $AUC_{0-inf}$ , respectively, and 17% and 24.5% decreases in [*S,S*]-hydroxylated bupropion  $C_{max}$  and  $AUC_{0-t}$ , respectively (Figure 2B, Table 2). The  $AUC_{0-t}$  metabolite/parent ratio increased from 88.7% to 124%.

**Safety.** The safety findings for the DDI studies are summarized in Table 3. There were no severe AEs, deaths, serious AEs, or AEs leading to study withdrawal. Across the studies, 4 subjects experienced sleep paralysis; in all cases, the AE occurred within 1 hour of lemborexant dosing, was mild in severity, resolved, and



**Figure 3.** Plasma midazolam (A), S-bupropion (B), and [S,S]-hydroxylated bupropion (C) concentration-time profiles after single-dose midazolam 2 mg + bupropion 75 mg or midazolam 2 mg + bupropion 75 mg + lemborexant 10 mg. Data are mean (standard deviation).

did not lead to study drug discontinuation. There were no clinically important changes in laboratory values, vital signs, electrocardiograms, or physical examination findings.

## Discussion

These are the first published analyses of the CYP3A and CYP2B6 DDI potential of lemborexant. Interactions between lemborexant and strong and moderate CYP3A inhibitors (itraconazole and fluconazole, respectively), a strong CYP3A inducer (rifampin), and CYP3A (midazolam) and CYP2B6 (bupropion) substrates were evaluated. Overall, the results of these assessments indicated that CYP3A inhibition increased lemborexant exposure, whereas CYP3A induction resulted in decreased lemborexant exposure. Concomitant use of lemborexant had an inductive effect on CYP2B6 substrates. In contrast, lemborexant had no clinically relevant effects on the PK of CYP3A.

In phase 1 studies, coadministration of lemborexant 10 mg with either a strong CYP3A inhibitor (itraconazole) or a moderate CYP3A inhibitor (fluconazole) increased lemborexant AUC by approximately 4-fold and  $C_{max}$  by 1.5-fold. Given these findings, a physiologically based pharmacokinetic (PBPK) model simulation was carried out to evaluate a dose recommendation for lemborexant coadministration with either a moderate or a strong CYP3A inhibitor (full PBPK model methodologies and results will be reported separately).

Specifically, lemborexant 2.5 mg exposure with fluconazole and itraconazole was simulated (assuming dose linearity of lemborexant) and compared with exposure with lemborexant 10 mg alone. Although the predicted  $C_{max}$  values of lemborexant 2.5 mg when coadministered with fluconazole and itraconazole were lower than those for lemborexant 10 mg (Supplementary Figures S1 and S2), these values were similar to the individual  $C_{max}$  values observed for lemborexant 5 mg in phase 1 study 001. As lemborexant 5 mg has demonstrated efficacy,<sup>5</sup> lemborexant 2.5 mg coadministered with a moderate or strong CYP3A inhibitor therefore is expected to be efficacious.

In this study, the effects of moderate and strong CYP3A inhibition on lemborexant exposure were investigated; given the study outcomes, the potential effect of weak inhibitors on lemborexant exposure is also of clinical interest. PBPK modeling has proven useful in supplementing *in vivo* clinical data and was further used to examine the effect of weak CYP3A inhibition on lemborexant exposure (full PBPK model methodologies and results will be reported separately). The PBPK model predicted a <2-fold effect on lemborexant exposure when the weak CYP3A inhibitors fluoxetine or ranitidine are coadministered with lemborexant. Overall, these findings support the conclusion that the maximum recommended dose when coadministered with weak CYP3A inhibitors is 5 mg.

Coadministration of lemborexant with a strong CYP3A inducer (rifampin) decreased lemborexant

**Table 2.** Midazolam and Bupropion PK Parameters After Single-Dose Administration When Coadministered With Lemborexant

Midazolam 2 mg + Bupropion 75 mg + Lemborexant 10 mg

PK Parameter	Geometric LSM		
	Midazolam + Bupropion (n = 27)	Midazolam + Bupropion + Lemborexant (n = 28)	Geometric Mean Ratio (90%CI)
<b>Midazolam</b>			
AUC <sub>0-t</sub> , ng·h/mL	20.2	22.9	1.133 (1.025–1.253)
AUC <sub>0-inf</sub> , ng·h/mL	21.4	24.1	1.130 (1.023–1.247)
C <sub>max</sub> , ng/mL	9.02	10.2	1.126 (1.026–1.236)
<b>S-bupropion</b>			
AUC <sub>0-t</sub> , ng·h/mL	76.8	42.4	0.553 (0.517–0.590)
AUC <sub>0-inf</sub> , ng·h/mL	87.3 <sup>a</sup>	47.6 <sup>b</sup>	0.545 (0.501–0.592)
C <sub>max</sub> , ng/mL	17.2	8.60	0.501 (0.454–0.552)
<b>[S,S]-hydroxylated bupropion</b>			
AUC <sub>0-t</sub> , ng·h/mL	70.5	53.2 <sup>c</sup>	0.755 (0.661–0.862)
C <sub>max</sub> , ng/mL	7.93	6.57 <sup>c</sup>	0.829 (0.759–0.905)

AUC<sub>0-inf</sub>, area under the concentration-time curve from zero time extrapolated to infinity; AUC<sub>0-t</sub>, area under the concentration-time curve from zero time to time of last measurable concentration; CI, confidence interval; C<sub>max</sub>, maximum observed concentration; LSM, least-squares mean; PK, pharmacokinetic.

<sup>a</sup>n = 25.

<sup>b</sup>n = 20.

<sup>c</sup>n = 27.

C<sub>max</sub> and AUC<sub>0-inf</sub> by more than 90%. This decrease in exposure is expected to result in markedly decreased efficacy. Therefore, the use of moderate and strong CYP3A inducers with lemborexant should be avoided.

In addition, estimated lemborexant exposures in subjects from studies 303 and 304 who were coadministered weak CYP3A inhibitors (fluoxetine, ranitidine, chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranolazine, tacrolimus, or ticagrelor; n = 15) showed an average 30% higher (420 versus 330 μg·h/L) exposures compared with subjects who were not coadministered weak CYP3A inhibitors (n = 257). The results of this exploratory population PK model<sup>5</sup> comparison should be interpreted with caution because of the small sample size and the lack of complete posology information for all subjects coadministered weak CYP3A inhibitors across the studies. Despite the caveats, these results suggest a degree of CYP3A inhibition (1.3-fold) in the general range of that predicted using the PBPK approach, informed by lemborexant studies with moderate CYP3A inhibitors.

Clinical DDI evaluation also showed that lemborexant did not have an effect on exposure to the sensitive CYP3A substrate midazolam. This finding is consistent with the in vitro findings regarding lemborexant and CYP3A inhibition (unpublished

data). Thus, lemborexant is not expected to have a clinically relevant effect on exposure to CYP3A substrates.

Lemborexant resulted in approximate 0.5-fold decreases in the C<sub>max</sub> and AUC<sub>0-inf</sub> of S-bupropion, a sensitive CYP2B6 substrate. Whereas this level of decrease in exposure may not be clinically relevant, concomitant use of lemborexant may lead to a decrease in the efficacy of CYP2B6 substrates and therefore would need to be monitored.

The finding that lemborexant did not have an inductive effect on midazolam, but had a small effect on bupropion, likely reflects the understanding that induction of CYP2B6 is regulated not only by the pregnane X receptor (PXR), but also by the constitutive androstane receptor (CAR).<sup>7,8</sup> PXR activators induce CYP2B6 as well as CYP3A4. CAR activators also induce CYP2B6 and show greater activation of CYP2B6 gene expression than PXR activators.<sup>8</sup> Considering the outcomes of our DDI studies with midazolam and bupropion, lemborexant may have a greater activation effect on CAR than PXR.

Lemborexant was generally well tolerated in the phase 1 studies. The overall safety profile was consistent with that reported in other clinical studies of lemborexant.<sup>2,3,9</sup>



**Table 3.** Summary of Treatment-Emergent AEs in Lemborexant Phase I DDI Studies

AE, n (%)	Itraconazole		Rifampin		Fluconazole		Midazolam + Bupropion	
	Lemborexant <sup>a</sup> (N = 15)	Lemborexant + Itraconazole <sup>b</sup> (N = 15)	Lemborexant <sup>a</sup> (N = 15)	Lemborexant + Rifampin <sup>b</sup> (N = 15)	Lemborexant <sup>c</sup> (N = 14)	Lemborexant + Fluconazole <sup>d</sup> (N = 14)	Midazolam + Bupropion <sup>e</sup> (N = 28)	Midazolam + Bupropion + Lemborexant <sup>f</sup> (N = 28)
AEs	1 (6.7)	4 (26.7)	4 (26.7)	2 (13.3)	3 (21.4)	3 (21.4)	2 (7.1)	1 (3.6)
Mild	1 (6.7)	4 (26.7)	4 (26.7)	2 (13.3)	3 (21.4)	3 (21.4)	1 (3.6)	1 (3.6)
Moderate	0	0	0	0	0	0	1 (3.6)	0
Severe	0	0	0	0	0	0	0	0
Treatment-related AEs	1 (6.7)	3 (20.0)	2 (13.3)	1 (6.7)	3 (21.4)	3 (21.4)	2 (7.1)	1 (3.6)
SAEs	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
AEs leading to study discontinuation	0	0	0	0	0	0	0	0

AE, adverse event; DDI, drug-drug interaction; SAE, serious adverse event.

<sup>a</sup>Days 1-14 (after a single dose of lemborexant on day 1 and throughout the 14-day washout period).

<sup>b</sup>Days 22-35 (after a single dose of lemborexant on day 22 and continued [starting on day 15] administration of rifampin or itraconazole through day 34).

<sup>c</sup>Days 1-10 (after a single dose of lemborexant on day 1 and throughout the 10-day washout period).

<sup>d</sup>Days 15-26 (after a single dose of lemborexant on day 15 and continued [starting on day 11] administration of fluconazole through day 26).

<sup>e</sup>Days 1-7 (after a single dose of midazolam and a single dose of bupropion on day 1 and throughout the 7-day washout period).

<sup>f</sup>Days 17-21 (after repeat single doses of midazolam and bupropion on day 17 and continued [starting on day 8] dosing with lemborexant through day 20).

## Conclusions

The findings from these analyses indicate that, at clinically relevant concentrations following daily dosing up to 10 mg, lemborexant is neither an inhibitor nor inducer of CYP3A, but has the potential to induce CYP2B6. As expected, given lemborexant is predominantly metabolized by CYP3A, moderate and strong CYP3A inhibitors and inducers modulated the PK of lemborexant. Specifically, coadministration of moderate or strong CYP3A inhibitors increased lemborexant exposure, whereas coadministration of a strong CYP3A inducer decreased lemborexant exposure. Overall, the clinical findings were consistent with the in vitro study findings. Patients taking lemborexant 5- or 10-mg doses should avoid coadministration with moderate and strong CYP3A inhibitors and inducers. Physicians should consult their local prescribing information for complete guidance on lemborexant dosing when administered with CYP3A inhibitors.

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## Conflicts of Interest

All authors are employees of Eisai Inc., Eisai Co., Ltd, or Eisai Ltd.

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## Data-Sharing Statement

Deidentified subject data that underlie the results reported in this article will not be made available, but summary information will be made available on ClinicalTrials.gov.

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## 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.