Physiologically-based pharmacokinetic modeling to predict drug interactions of lemborexant with CYP3A inhibitors

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Abstract

Lemborexant, a recently approved dual orexin receptor antagonist for treatment of adults with insomnia, is eliminated primarily by cytochrome P450 (CYP)3A metabolism. The recommended dose of lemborexant is 5 mg once per night, with a maximum recommended dose of 10 mg once daily. A physiologically-based pharmacokinetic (PBPK) model for lemborexant was developed and applied to integrate data obtained from in vivo drug–drug interaction (DDI) assessments, and to further explore lemborexant interaction with CYP3A inhibitors and inducers. The model predictions were in good agreement with observed pharmacokinetic data and with DDI results from clinical studies with CYP3A inhibitors, itraconazole and fluconazole. The model further predicted that DDI effects of weak CYP3A inhibitors (fluoxetine and ranitidine) are weak, and effects of moderate inhibitors (erythromycin and verapamil) are moderate. Based on the PBPK simulations and clinical efficacy and safety data, the maximum daily recommended lemborexant dose when administered with weak CYP3A inhibitors is 5 mg; co-administration of moderate and strong inhibitors should be avoided except in countries where 2.5 mg has been approved.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
CYP3A4 is the predominant enzyme involved in the metabolism of lemborexant.

WHAT QUESTION DID THIS STUDY ADDRESS?
The potential for drug-drug interactions with moderate and weak CYP3A inhibitors when administered with lemborexant.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
A physiologically-based pharmacokinetic (PBPK) model for lemborexant integrating in vitro and clinical data has been successfully developed. PBPK simulations confirm the observed moderate (<5-fold) changes in lemborexant exposure when co-administered with various moderate and strong CYP3A inhibitors. PBPK simulations predicted weak changes (<2-fold) in lemborexant exposure when co-administered with weak CYP3A inhibitors.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Lemborexant should either not be co-administered with moderate and strong CYP3A inhibitors or should not exceed 2.5-mg doses (if 2.5 mg is approved in the patient's country), whereas a lemborexant maximum dose of 5 mg would be appropriate for patients prescribed weak CYP3A inhibitors.

INTRODUCTION

Insomnia disorder, defined as difficulty initiating and/or maintaining sleep for greater than or equal to 3 nights a week for greater than or equal to 3 months, has a prevalence of ~10% in the general population.[1] Lemborexant (also referred to as E2006), a recently approved orally active dual orexin receptor antagonist, improves both sleep onset and sleep maintenance in adults (≥18 years) with insomnia disorder.[2] The recommended dose of lemborexant is 5 mg once per night, but this may be increased to 10 mg based on clinical response and tolerability. The efficacy and safety of lemborexant have also been demonstrated in patients 65 years of age and older.[3,4]

Insomnia disorder is often comorbid with a range of other medical or psychiatric disorders.[1,5] Approximately 40% of all patients with insomnia have a co-existing psychiatric condition, with depression being the most common.[6] Moreover, prevalence and severity of insomnia disorder increases with age, with up to 93% of people having one or more comorbid conditions or other risk factors, including heart disease, stroke, and diabetes.[7,8] Management of insomnia with comorbid conditions may require the use of multiple pharmacologic therapies. Furthermore, sleep complaints have been associated with the use of an increasing number of nonprescription medications.[9] These factors may increase the risk of potential drug–drug interactions (DDIs) with lemborexant in patients with insomnia.

Several clinical drug-interaction and metabolism studies were conducted to inform our understanding of potential DDI liabilities of lemborexant. A human mass-balance study (E2006-A001-007 [NCT02046213]) and in vitro metabolism studies have demonstrated that lemborexant is eliminated mainly via metabolism mediated by cytochrome P450 (CYP)3A in the liver with minimal contribution of intestinal metabolism.[10,11] Clinical DDI studies (study overview in Table S1) with strong and moderate CYP3A inhibitors (itraconazole, E2006-A001-004 [NCT02085967] and fluconazole, E2006-A001-012 [NCT03451110], respectively) and a strong inducer (rifampicin [E2006-A001-004]) demonstrated that inhibition or induction of CYP3A affected the pharmacokinetics (PK) of lemborexant.[10] Co-administration of lemborexant 10 mg with itraconazole 200 mg q.d. increased lemborexant maximum plasma concentration (C_{max}) by 1.36-fold and the area under the plasma concentration–time curve from zero time to infinity ($AUC_{(0-inf)}$) by 3.70.[12] Notably, the co-administration

of lemborexant 10 mg with the moderate inhibitor fluconazole 200 mg q.d. resulted in similar outcomes (i.e., a 1.6-fold increase in C_{max} and a 3.8-fold increase in the AUC of lemborexant from zero time to the time of last quantifiable concentration [$AUC_{(0-t)}$]).[10] Conversely, co-administration with rifampicin 600 mg q.d. reduced the C_{max} and $AUC_{(0-inf)}$ of lemborexant by 92% and 97%, respectively.[10]

Based on these findings, additional evaluation of the potential for lemborexant DDI with moderate and weak CYP3A inhibitors is warranted to better inform healthcare providers and patients on potentially clinically important concomitant medication use. To complement the existing lemborexant clinical DDI information, we developed a physiologically-based pharmacokinetic (PBPK) model incorporating in vitro data on plasma protein binding, information on physicochemical properties, and human oral clearance data. This PBPK modeling approach has been used previously to inform drug labels, and is recognized by the European Medicines Agency and the US Food and Drug Administration (FDA) as an appropriate tool for DDI predictions in the absence of complete clinical trial data.[13-18]

The objectives of this work were to develop and verify a PBPK model for lemborexant using the Simcyp population-based simulator,[19] and to apply the model to predict DDIs of lemborexant with additional moderate and weak inhibitors of CYP3A. These predictions were to provide considerations for lemborexant dosing when co-administered with known CYP3A inhibitors.

METHODS

Clinical studies

Data from six clinical studies of lemborexant in healthy individuals were used to develop, verify, and validate the PBPK model. Relevant details of the studies are presented below and summarized in Table S1.

The mass-balance study (E2006-A001-007 [NCT02046213])[11] was an open-label, single-dose study to determine the metabolism and excretion of [14C]lemborexant in healthy male individuals. [14C]Lemborexant was administered at 10 mg as a capsule, and the concentration of lemborexant in the urine and feces was measured up to 35 days post-dose. The single ascending dose study (E2006-A001-001

[NCT01463098]) was a two-part, two-center, randomized, double-blind study with placebo- and active-control design.[20] In part A, 64 healthy individuals received single oral daily doses of lemborexant of 1, 2.5, 5, 10, 25, 50, 100, or 200 mg. The sequential multiple ascending dose study (E2006-A001-002 [NCT01673451]) was a two-part, single-center, randomized, double-blind, placebo-controlled study.[20] In part A, 48 healthy individuals received multiple oral daily doses of lemborexant 2.5, 5, 10, 25, 50, or 75 mg.

Two studies (E2006-A001-004 and E2006-A001-012) assessed DDI of lemborexant with strong and moderate modulators of CYP3A, respectively.[10] Study 004 was a two-part, single-center, open-label study to evaluate DDI of lemborexant when administered with CYP3A substrates. Part A assessed DDI with itraconazole and rifampicin in 30 healthy individuals (15 per drug). The individuals received a single oral dose of lemborexant (immediate release [IR] formulation) 10 mg alone, then itraconazole 200 mg q.d. for 20 days or rifampicin 600 mg q.d. for 20 days, followed by a single dose of lemborexant co-administered with itraconazole or rifampicin. Study 012 was a single-center, open-label study. Part 3 of the study evaluated DDI with fluconazole in 14 healthy individuals. The individuals received a single oral dose of lemborexant 10 mg alone, then a single oral dose of fluconazole 400 mg followed by fluconazole 200 mg q.d. for 15 days, and a subsequent single dose of lemborexant co-administered with fluconazole. The food effect study (E2006-A001-008 [NCT02089412]) was an open-label, single-dose, randomized crossover study in 22 healthy individuals who received a single oral dose of lemborexant 10 mg in fed (a standard high-fat meal) and fasted conditions.

PBPK modeling strategy

A PBPK model for lemborexant was developed using Simcyp version 17r1 simulator (Certara) and refined using available in vitro and in vivo clinical data. The overall PBPK modeling and simulation analysis framework adopted for predicting DDIs with lemborexant is summarized in Figure 1 and is aligned with Shebley et al.[17] A summary of the criteria for assessing the lemborexant PBPK model performance and credibility under the context of use, as per Kuemmel et al.,[21] is presented in Table S2.

Model development

Physicochemical information, absorption parameters, distribution, metabolism, and excretion data from in vitro and clinical studies, and in vitro dissolution profiles of the IR formulation were used in the development of the PBPK model. Details of the key input parameters are described below and summarized in Table 1.
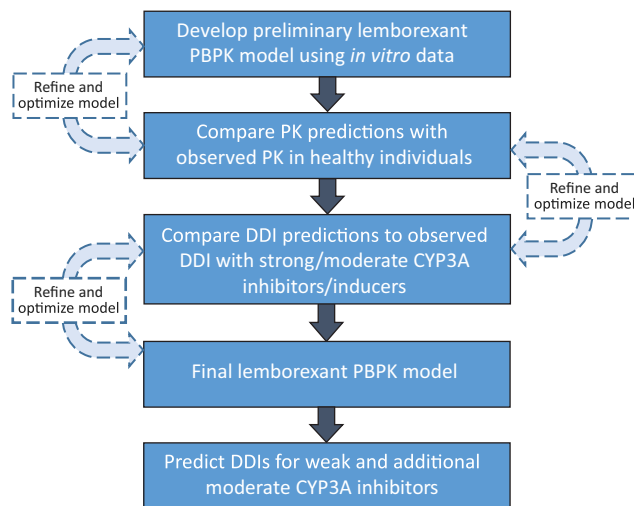

FIGURE 1 Overall steps of model development/verification and application to DDI predictions. DDI, drug–drug interaction; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics

Physicochemical and binding parameters

Lemborexant has a molecular weight of 410.42 g/mol. The logarithm of the octanol:water partition coefficient (log P) measured at 25°C was 3.7. Lemborexant is a weak basic compound, and the negative logarithm of the acid dissociation constant (pKa) measured by a capillary electrophoresis method was less than 3.5, which was out of the recommended measurement range (≥ 3.5) in the assay. Thus, a value of 3.5 was used as input.

In human plasma, the in vitro plasma protein binding of lemborexant was 87.4–88.7% bound with no reported concentration dependency in the range of 100–1000 ng/ml.[11] Lemborexant was primarily bound to human serum albumin, low-density lipoprotein, and high-density lipoprotein (unpublished data reported by Eisai Inc.). The human blood to plasma concentration ratio (B:P) of lemborexant was reported to be 0.610 to 0.656 in the concentration range of 100–1000 ng/ml (unpublished data reported by Eisai Inc.). Based on these data, the fraction unbound in plasma (fu) of 0.113 and a B:P value of 0.636 were assumed to be constant, and human serum albumin was considered as a main binding protein in plasma.

Formulation, permeability, and absorption

Initial iterations of the PBPK model used a solution of lemborexant as the formulation input, and therefore did not require additional data regarding solubility or dissolution. Across the clinical studies underpinning this model, lemborexant was administered as an oral capsule in the single ascending dose study, multiple ascending dose study, and a

TABLE 1 Input parameter values

Parameter	Input value/option	Source/reference and notes
Molecular weight	410.42	https://www.ciaaw.org/atomic-weights.htm
Compound type	Monoprotic base	Unpublished data reported by Eisai Inc.
Log P	3.7	Unpublished data reported by Eisai Inc.
pKa	3.5	Unpublished data reported by Eisai Inc.
B:P	0.636	Mean value was calculated using unpublished data reported by Eisai Inc.
Fu	0.113	Mean value based on lemborexant 100 ng/ml using data reported by Ueno et al.[11]
Main binding protein in plasma	Albumin	See "Model development" section
Absorption model	ADAM	Simcyp's ADAM model[22]
fu_{gut}	1.0	Assumption
P_{eff}	8.799×10^{-4} cm/s	Predicted using mechanistic P_{eff} model in Simcyp
Formulation	Solution or solid; IR tablet	See "Model development" section
Dissolution[a]	Dissolution profiles at pH 1.2 and 6.8 for stomach and small intestine, respectively	Landry et al.[38]
V_{ss} (L/kg)	12.914	Predicted value in Simcyp using the full PBPK, method 2
Kp scalar	0.51	Estimated from unpublished individual plasma concentration data reported by Eisai Inc.
CL_{int} input, μL/min/pmol protein, CYP3A4	Recombinant enzyme kinetics 0.4684	CL_{int} obtained with Simcyp's retrograde calculator from CL/F of 32.8 L/h, f_a of 0.87 (based on Ueno et al.[11]), and assumed f_g of 1
fu_{mic}	1.0	Fixed to 1.0 since input of CL_{int} was obtained from retrograde calculation
CL_{ren}, L/h	0	Ueno et al.[11]
Metabolic interactions	None	See "Model development" section

Abbreviations: ADAM, Advanced Dissolution, Absorption, and Metabolism; B:P, blood-to-plasma partition ratio; CL/F, apparent oral clearance; CL_{int}, intrinsic clearance; CL_{ren}, renal clearance; f_a, fraction of the oral dose absorbed; f_u, fraction unbound in plasma; fu_{gut}, fraction unbound in enterocytes; fu_{mic}, fraction unbound in microsomes; IR, immediate release; Kp, tissue to plasma partition coefficient; Log P, logarithm of the octanol:water partition coefficient; PBPK, physiologically-based pharmacokinetic; P_{eff}, effective membrane permeability in humans; pKa, logarithm of the acid dissociation constant; V_{ss}, volume of distribution at steady state.

[a]In vitro dissolution profiles of IR tablets to reflect profiles of immediate-release tablets in different pH buffers were inputted to reflect the influence of pH on dissolution of IR tablets. pH solubility data were not used in the model.

human mass-balance study, and as an IR 10-mg tablet in the DDI studies with itraconazole, fluconazole, and rifampicin, and the food effect study. Subsequent model refinements for predicting the PK profiles of lemborexant as well as DDIs used the Advanced Dissolution, Absorption, and Metabolism model,[22] wherein the dissolution profiles of the IR lemborexant tablet were incorporated.

The dissolution profiles of IR tablets were assessed in vitro at pH 1.2 and pH 6.8, in accordance with the Japanese Pharmacopoeia. The United States Pharmacopeia apparatus 2 was used, with 900 ml buffer volume per vessel and a paddle revolution speed of 50 rpm at $37.0 \pm 0.5°C$ (Table S3). The dissolution profiles at pH 1.2 and 6.8 were entered as fasted stomach and intestinal dissolution data, respectively. The effective membrane permeability (P_{eff}: 8.799×10^{-4} cm/s) was predicted with the Simcyp Mechanistic P_{eff} (MechPeff) model based on the log P of lemborexant.

Volume of distribution

The volume of distribution at steady state of lemborexant was estimated by the full perfusion-limited distribution method (method 2) in Simcyp with predicted tissue to plasma partition coefficient (Kp) values. The Kp scalar input in the model was determined to be 0.51 by parameter estimation using observed plasma concentration–time profile from the human mass-balance study.

Elimination

To identify the metabolic enzymes responsible for lemborexant metabolism in humans, in vitro studies using recombinant human CYPs and cryopreserved human hepatocytes were performed (unpublished data reported by Eisai Inc.). After incubation with each recombinant human CYP isoform (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, and 4F12) at 37°C for 20 min, the highest level of lemborexant metabolism was found with CYP3A4 (residual ratio: 30%), and no or minimal metabolic activity was detected for the other CYP isoforms tested (residual ratio: ≥81%). In addition, lemborexant metabolism in human hepatocytes was completely inhibited by 1-aminobenzotriazole, a nonspecific CYP inhibitor, and the CYP3A4 inhibitors, troleandomycin and ketoconazole. These results suggested that lemborexant is metabolized predominantly by CYP3A4, with negligible contributions from other CYP isoforms. The fraction of metabolism assigned to CYP3A4 was therefore set as 100% in the model. The CYP3A4 intrinsic clearance (CL_{int}) used in the model, 0.4684 µl/min/pmol protein, was obtained using the Simcyp retrograde calculator.[23] This value was calculated based on lemborexant apparent oral clearance of 32.8 L/h and the fraction of the oral dose absorbed (f_a) of 0.87 obtained from the human mass-balance study and was entered as a CL_{int} value from recombinant enzyme kinetics, with an unbound fraction in the assay incubation of 1.0. In the human mass-balance study, unchanged lemborexant was not detected in urine, but was detected as a major component in feces (13.0% of dose). Considering no detection of glucuronide metabolites formed by direct conjugation of lemborexant in humans and no biliary excretion of lemborexant in rats, unchanged lemborexant detected in feces would be attributed to the unabsorbed fraction of lemborexant. Therefore, the f_a of lemborexant was assumed to be 0.87. The fraction of absorbed drug that escapes first-pass gut metabolism was assumed to be 1.0 and used only for the retrograde calculation. In addition, renal clearance was assumed to be zero in the model.

Interactions

Lemborexant demonstrated weak time-dependent inhibition on CYP3A and weak inductive effects on CYP3A4 and CYP2B6 in vitro (unpublished data reported by Eisai Inc.), and it was confirmed in vitro that transport of lemborexant via P-glycoprotein and breast cancer resistance protein was negligible.[11] In order to investigate DDI effects of lemborexant on CYP3A and CYP2B6, healthy adult subjects received lemborexant 10 mg q.d. for 13 days and midazolam (2 mg) and bupropion (75 mg) on day 10.[10] Plasma exposures of midazolam, a typical CYP3A substrate, and S-bupropion, a CYP2B6 substrate, were then evaluated.

In these DDI investigations, multiple doses of lemborexant did not affect plasma exposures of midazolam, but decreased plasma exposures of S-bupropion by 45.5%.[10] Thus, at the maximum therapeutic dose (10 mg), lemborexant is neither an inhibitor nor inducer of CYP3A, but has a weak potential to induce CYP2B6. Because the objective of this work was to assess DDIs mediated by CYP3A, information regarding inhibition of CYP3A and induction of CYP3A and CYP2D6 was not incorporated into the PBPK model for lemborexant.

Model verification and validation

Simulation of lemborexant PK in healthy individuals

Simulations of lemborexant PK in healthy individuals were performed using the simulation designs listed in Table S4. Simcyp's default Healthy Volunteer population (Sim-Healthy) comprised of 100 individuals (10 trials of 10 participants each) was used. Single oral doses of 2.5 mg, 10 mg, or 100 mg, or multiple 10-mg doses were administered with 250 ml of water under either fasted or fed conditions.

The concordance of the PBPK model predictions and observed PK profiles of lemborexant was evaluated by overlaying the mean model-predicted profiles and the 5th and 95th percentiles onto the observed individual lemborexant profiles. The prediction was considered successful if the mean predicted profile and the 90% prediction interval were in overall agreement with the observed PK profiles of lemborexant. In addition, the geometric mean exposures calculated from each simulation were compared with those reported in each corresponding clinical study. An adequate prediction was achieved if the predicted exposure parameter fell within two-fold of the observed value.[24-28]

Simulation of tested DDI

Simulations to predict the clinically observed DDIs of lemborexant with the strong CYP3A inhibitor itraconazole, the moderate inhibitor fluconazole, or the strong CYP3A inducer rifampicin, were run in the Sim-Healthy volunteer population (Table S5), following the FDA guidance on assessment of DDIs.[18]

Simulations with itraconazole included the CYP3A inhibitory contribution of its metabolite, hydroxy-itraconazole (OH-itraconazole). In all simulations, the inhibitor/inducer dosing started on day 1 and continued for the full duration of the simulation. A single 10 mg oral dose of lemborexant was administered with 250 ml of water under fasted conditions on day 8 in all simulations except for DDI simulations with

fluconazole (day 5). All inhibitor and inducer compound files used for the simulations were the default compound files provided within Simcyp except for itraconazole and OH-itraconazole, which were provided by the IQ Consortium Itraconazole PBPK working group.[29] The IQ itraconazole compound files were better aligned with the dosing conditions of the clinical DDI trial (fasted capsule) and produced simulations that were better aligned with the observed DDI results compared with the default Simcyp itraconazole compound files.

The magnitude of the DDI was measured as the ratio of the $AUC_{(0-t)}$ in the presence and absence of an inhibitor or inducer (AUCR). The ratio of C_{max} ($C_{max}R$) was also calculated. The magnitude of the predicted AUCR was used to determine the overall risk of DDI in accordance with the FDA Guide on Drug Interactions Studies.[18] A negligible inhibitory effect was defined as less than 1.25 change in exposure, a weak effect as greater than or equal to 1.25 to less than 2-fold change; a moderate effect as greater than or equal to 2- to less than 5-fold change, and a strong effect as a greater than or equal to 5-fold change. Weak, moderate, and strong inducers were defined as those that decreased AUC by greater than or equal to 20 to less than 50%, greater than or equal to 50 to less than 80%, and greater than or equal to 80%, respectively.[18]

The adequacy of the AUCR prediction for each DDI simulation was assessed by comparing the predicted AUCR, calculated by Simcyp, with the observed AUCR from the two DDI clinical studies (Table S1), using the approach proposed by Guest et al.[30] This method consists of calculating an acceptable prediction range (i.e., the upper and lower limits of acceptable values for the predicted AUCR), which take into account the observed variability of the AUC, instead of using a fixed twofold error criterion that has been traditionally used for evaluating prediction adequacy.[24-28]

Model application

Prediction of DDI with weak and moderate CYP3A inhibitors

Simulations to predict untested DDIs of lemborexant with moderate CYP3A inhibitors (erythromycin and verapamil) and weak CYP3A inhibitors (fluoxetine and ranitidine) were run with the Sim-Healthy volunteer population (Table S5).

Simulations with fluoxetine and verapamil included the CYP3A inhibitory contribution of their metabolites, norfluoxetine, and norverapamil, respectively. Default compound files provided within Simcyp were used for all inhibitors, except for ranitidine, which used a compound file developed by a Simcyp Consortium group member, available for download in the Compound and Population Repository of the Simcyp members' account site.

A single 10 mg oral dose of lemborexant was administered with 250 ml of water under fasted conditions on day 8 in all simulations except for DDI simulations with fluoxetine (day 25). Simulations were run as described above, and the magnitude of the DDI was determined according to the FDA guidelines.[18]

RESULTS

Model validation

Prediction of PK compared with observed values

Simulated PK profiles and predicted lemborexant PK parameters were generally in good agreement with observed data under fasted conditions and were in general within the defined acceptance criteria (Figure 2, Table 2). The lemborexant C_{max} values were slightly underestimated (fold difference range: 0.46–0.85) for the 2.5-mg and 10-mg doses compared with observed data from the single ascending dose and DDI studies. However, only lemborexant 2.5 mg oral solution and lemborexant 10 mg IR formulation (tablet) exceeded the twofold threshold for adequate prediction (fold difference of 0.46 and 0.47, respectively; Table 2). In the multiple ascending dose study, C_{max} values were well predicted following multiple doses of lemborexant 10 mg. The predicted $AUC_{(0-t)}$ values were in good agreement with the observed values across all doses and studies.

In the food effect study (study 008), although the predicted C_{max} was lower than observed C_{max}, and exceeded the twofold threshold, the ratios of C_{max} and $AUC_{(0-inf)}$ for the fasted and fed conditions were well predicted (fold differences: $C_{max}R = 0.768$; AUCR = 0.837). The time to maximum concentration food effect delay was also well captured. Overall, these results suggest that the predictive performance of the lemborexant PK model is adequate.

Prediction of DDI compared with observed values

The PBPK model captured well the observed lemborexant PK profiles associated with itraconazole and fluconazole coadministration (Figure 3, Table 3). The predicted AUCR and $C_{max}R$ for itraconazole were 3.13 and 1.45, respectively, which were close to the observed values (3.58 and 1.36, respectively). Although the predicted AUCR and $C_{max}R$ values for fluconazole (2.83 and 1.37, respectively) were slightly smaller than the observed values (3.76 and 1.62, respectively), they were well within the acceptable prediction range (Table 3, Figure S1).

The model underpredicted the PK profile of lemborexant when the compound was co-administered with rifampicin (Figure 3, Table 3). Although the PBPK model predicted a
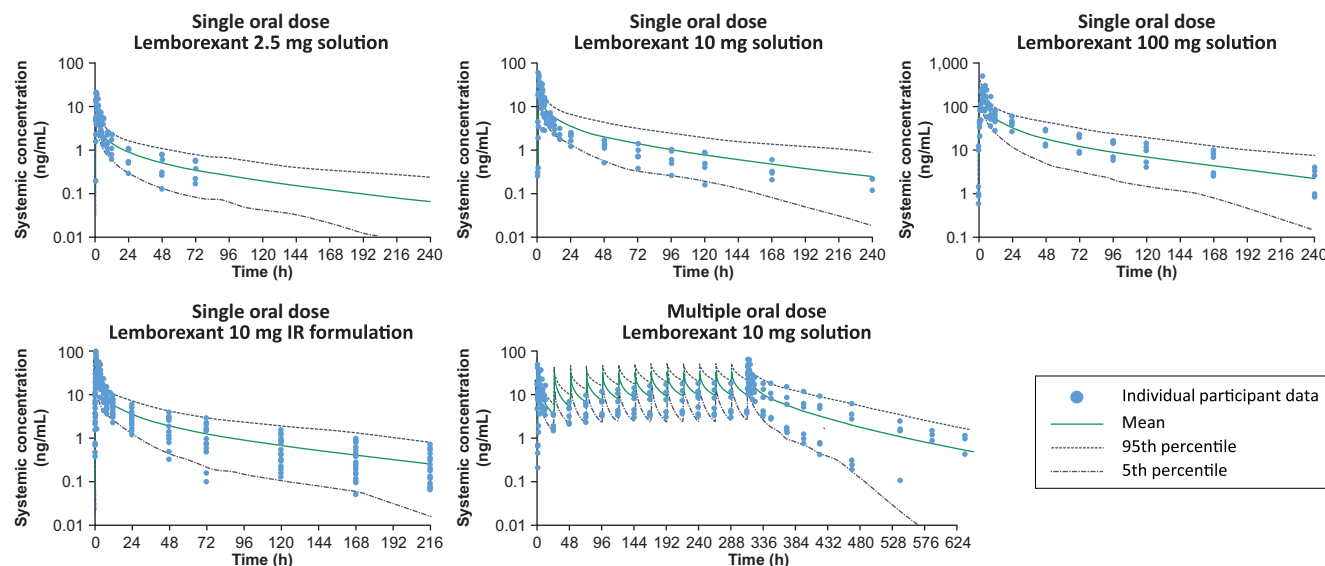
FIGURE 2 Predicted and observed plasma concentration–time profiles of lemborexant in healthy volunteers under fasted conditions. IR, immediate release

strong inductive effect of rifampicin on lemborexant PK, the predicted AUCR (0.19) was larger than the observed value (0.033) and outside the acceptable prediction range (0.017–0.065), thus indicating an underestimation of the observed rifampicin induction results.

Model application

Prediction of DDI with additional CYP3A inhibitors

The simulations of lemborexant with additional CYP3A inhibitors indicate that lemborexant is predicted to have moderate DDI with erythromycin and verapamil and weak DDI with fluoxetine and ranitidine (Table 4, Figure S1). Erythromycin is predicted to have the highest inhibitory potential on lemborexant (AUCR = 4.33, $C_{max}R$ = 1.46), followed by verapamil (AUCR = 3.87, $C_{max}R$ = 1.43), classifying these DDIs as moderate according to the FDA guidelines.[18] Fluoxetine is considered a weak CYP3A inhibitor, which was confirmed in simulations where AUC and C_{max} were slightly increased (AUCR = 1.77, $C_{max}R$ = 1.21). Similarly, co-administration with weak CYP3A inhibitor ranitidine is predicted to result in an AUCR of 1.54 and a $C_{max}R$ of 1.11.

DISCUSSION

Overall, the PBPK model-predicted PK profiles of lemborexant were in good agreement with the data observed across clinical studies. The prediction errors for the AUC values after oral administration of lemborexant were within the acceptable twofold margin. The observed clinical study DDI results with itraconazole and fluconazole were also well predicted by the model. These results indicate that the PBPK model for lemborexant was successfully developed and was suitable to predict DDIs due to CYP3A inhibition. Additional simulations of the impact of DDIs with untested CYP3A inhibitors on lemborexant PK predicted a moderate DDI with erythromycin and verapamil, and a weak DDI with fluoxetine and ranitidine.

Although the PBPK model predicted a strong inductive effect of rifampicin on lemborexant exposure, the predicted DDI effect of rifampicin was underestimated. One possible explanation for the underestimation of the rifampicin DDI is that the model underpredicted either plasma concentrations or the steady-state accumulation of rifampicin obtained in the clinical study, therefore underestimating its impact on lemborexant PK. Underprediction of the rifampicin induction effect has been attributed to available default rifampicin models used by PBPK software.[31] Cases of underprediction in the interaction of rifampicin and midazolam have also been previously reported using Simcyp.[32] Such bias can be corrected by including robust in vivo data to overcome innate inter-donor and inter-laboratory variability, and may be incorporated in future versions of the model.[32] Nonetheless, the predictions of the current model show a strong DDI with rifampicin, corroborating the recommendation based on the rifampicin clinical DDI study, which indicated that lemborexant should not be co-administered with strong CYP3A inducers.[10]

TABLE 2 Predicted and observed PK parameters of lemborexant

Single 2.5, 10, and 100 mg oral doses using solution formulation

	Observed parameter (capsule)			Predicted parameter (solution)			Fold difference, predicted/observed	
	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	$AUC_{(0-t)}$
Dose, mg	ng/ml	h	ng•h/ml	ng/ml	h	ng•h/ml		
2.5	14.9	1.01	74.4	6.79	1.06	66.4	0.46[a]	0.89
10	32.0	1.00	274	27.1	1.06	354	0.85	1.29
100	242	3.00	4,300	261	1.08	3,270	1.08	0.76

Single 10 mg oral dose using IR formulation

	Observed parameter, tablet			Predicted parameter, tablet			Fold difference, predicted/observed	
Dose, mg	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	$AUC_{(0-t)}$
10	54.3	1.00	411	25.3	1.06	327	0.47[a]	0.80

Multiple 10 mg oral doses using solution formulation

	Observed parameter, capsule			Predicted parameter, solution			Fold difference, predicted/observed	
Dose, mg	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	$AUC_{(0-t)}$
10, day 1	28.0	3.25	182	24.2	1.11	168	0.86	0.92
10, day 14	44.8	1.75	321	32.9	1.10	327	0.73	1.02

Single 10 mg oral dose with fed and fasted conditions using IR formulation

	Observed parameter, tablet			Predicted parameter, tablet			Fold difference, predicted/observed	
Dose, mg	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	T_{max}	$AUC_{(0-t)}$	C_{max}	$AUC_{(0-t)}$
10, fed	44.1	3.00	460	15.1	1.86	327	0.34	0.71
10, fasted	57.1	1.00	389	25.5	1.08	331	0.45	0.85

Note: C_{max} and $AUC_{(0-t)}$ values are expressed as geometric mean, and T_{max} values are expressed as median.

Abbreviations: $AUC_{(0-t)}$, area under the concentration–time curve from zero time to time of last quantifiable concentration; C_{max}, maximum concentration; IR, immediate release; PK, pharmacokinetic; T_{max} time at which the highest drug concentration occurs.

[a]Value greater than the 2-fold cutoff for acceptable prediction.

Clinical PK data and PBPK simulations were in agreement with respect to co-administration of lemborexant with CYP3A inhibitors. There was up to a 3.8-fold increase in AUCR when lemborexant was co-administered with strong and moderate CYP3A inhibitors (itraconazole and fluconazole). Interestingly, the DDI results with moderate inhibitor fluconazole were comparable with that of the strong inhibitor. To better understand and characterize the DDI risks of lemborexant co-administration with moderate CYP3A inhibitors, simulations were performed with two additional moderate inhibitors, erythromycin and verapamil. The simulation results with these additional moderate inhibitors were similar to those observed and predicted with fluconazole. Up to a 4.3-fold increase in AUC was predicted, thus reinforcing the notion that concomitant use of lemborexant 5 mg and 10 mg with either moderate or strong CYP3A inhibitors should be avoided.

A stand-alone clinical study was not conducted to evaluate DDI risk of lemborexant with weak CYP3A inhibitors. Therefore, PBPK simulations were conducted with 2 weak CYP3A inhibitors, fluoxetine and ranitidine, to assess this untested DDI scenario in lieu of clinical studies. The PBPK model predicted a weak DDI effect of both drugs (up to 1.77-fold increase in AUC) when co-administered with lemborexant 10 mg. These results suggest that lemborexant 5 mg may be co-administered with drugs that are known weak inhibitors of CYP3A.

The clinical consequence of the observed and predicted increases in lemborexant exposures in the presence of CYP3A inhibitors was evaluated in the context of the efficacy and safety profile of lemborexant across its therapeutic range, evaluated across a phase II study (E2006-G000-201 [NCT01995838][33]), two phase III studies (E2006-G000-304, SUNRISE-1 [NCT02783729][3];
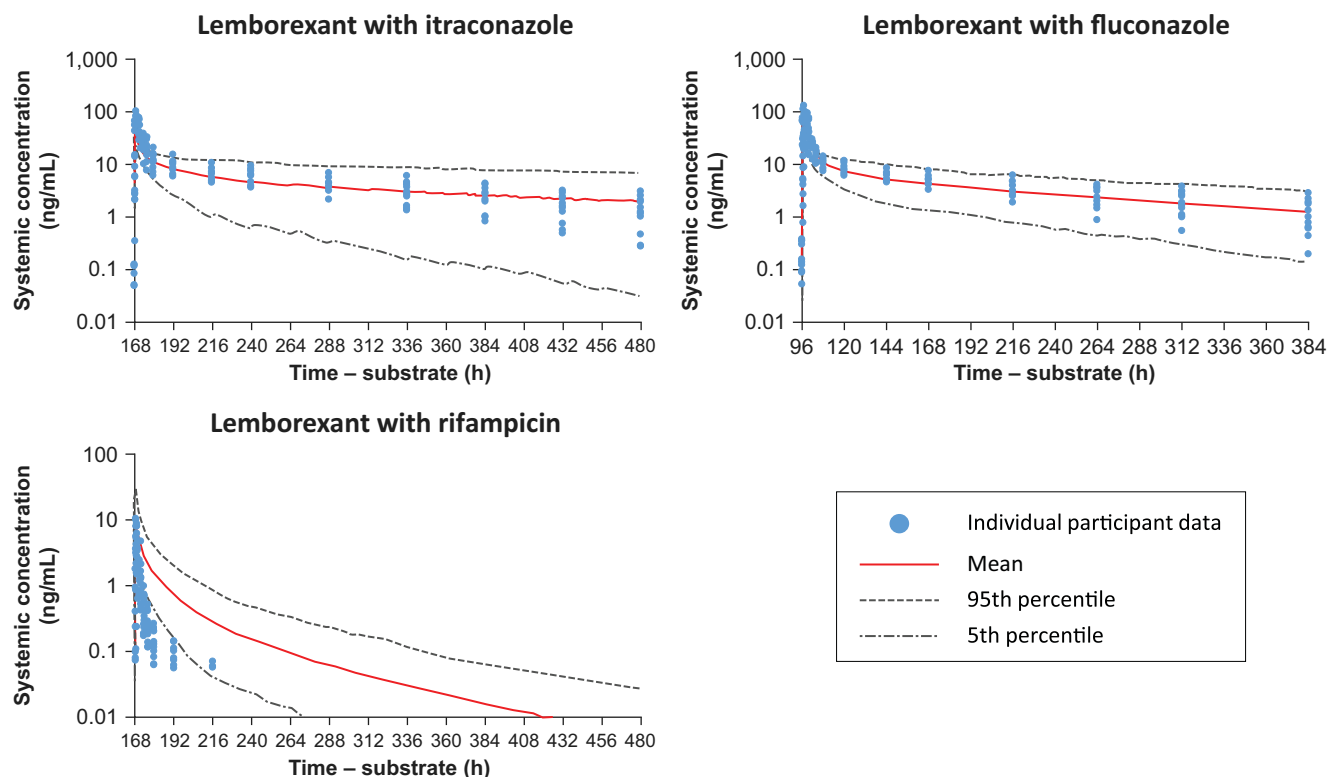
FIGURE 3 Predicted and observed plasma concentration–time profiles of lemborexant in healthy volunteers after co-administration with CYP3A4 inducers and inhibitors

TABLE 3 Observed and predicted mean AUCR and $C_{max}R$ for DDI simulations of lemborexant 10 mg with itraconazole, fluconazole, and rifampicin

Concomitant drug and dose	AUCR[a]		CV% of observed AUCR[b]	Acceptable prediction range[c]	$C_{max}R$[a]		Predicted DDI impact[d]
	Observed	Predicted			Observed	Predicted	
Itraconazole 200 mg q.d.	3.58	3.13	32.6	1.98–6.49	1.36	1.45	Moderate
Fluconazole 200 mg q.d.	3.76	2.83	15.3	2.12–6.67	1.62	1.37	Moderate
Rifampicin 600 mg q.d.	0.033	0.19[e]	49.1	0.017–0.065	0.085	0.38	Strong

Abbreviations: AUCR, ratio between the area under the concentration–time curve in the presence and absence of an inhibitor or inducer; $C_{max}R$, ratio between the maximum concentration in the presence and absence of an inhibitor or inducer; CV%, percent coefficient of variation; DDI, drug–drug interaction; FDA, US Food and Drug Administration.

[a]Geometric mean of observed and predicted AUCR or $C_{max}R$.

[b]Percent coefficient of variation around the geometric mean of the observed AUCR in clinical studies.

[c]Acceptable prediction range calculated as previously described.[30]

[d]DDI impact classification made in accordance with FDA DDI guidelines.[18]

[e]Predicted AUCR value is outside of the calculated acceptable prediction range.

and E2006-G000-303, SUNRISE-2 [NCT02952820][4]), and safety studies assessing next-day performance (residual effects) of lemborexant.[34,35] These studies demonstrated that doses of 5 mg and above provide clinically meaningful sleep benefits, and that lemborexant exposures greater than 10 mg were associated with an increased risk of somnolence adverse events.[33,36] With somnolence emerging as the most frequently occurring

treatment-emergent adverse event, PK/pharmacodynamic analyses of late-stage trials indicated that this, and other adverse events of interest, are exposure-independent over the 5–10 mg therapeutic dose range of lemborexant.[37]

Therefore, lemborexant exposures in a DDI scenario that are equivalent or above those achieved with lemborexant 10 mg alone are not expected to balance clinical benefit with

TABLE 4 Predicted geometric mean AUCR and $C_{max}R$ for DDI simulations of lemborexant with erythromycin, verapamil, fluoxetine, and ranitidine

Concomitant drug and dose	AUCR	$C_{max}R$	Predicted DDI impact[a]
Erythromycin 500 mg q6h	4.33 (4.03–4.66)	1.46 (1.42–1.50)	Moderate
Verapamil 80 mg t.i.d.	3.87 (3.59–4.17)	1.43 (1.40–1.46)	Moderate
Fluoxetine 40 mg q.d.	1.77 (1.69–1.84)	1.21 (1.19–1.23)	Weak
Ranitidine 150 mg b.i.d.	1.54 (1.49–1.60)	1.11 (1.10–1.12)	Weak

Note: Values represent geometric mean and 90% confidence interval.

Abbreviations: AUCR, ratio between the area under the concentration–time curve in the presence and absence of an inhibitor or inducer; $C_{max}R$, ratio between the maximum concentration in the presence and absence of an inhibitor or inducer; DDI, drug–drug interaction; FDA, US Food and Drug Administration.

[a]DDI impact classification made in accordance with FDA DDI guidelines.[18]

safety concerns adequately. Based on the results presented in this work, typical lemborexant exposures in individuals co-administered moderate and strong CYP3A inhibitors would likely well exceed the upper end of the therapeutic range (10 mg) even after a 5-mg dose of lemborexant. Hence, co-administration with moderate and strong CYP3A inhibitors is not recommended with lemborexant, or lemborexant doses in this scenario should not exceed 2.5 mg (in countries where this dose is approved). In contrast, the co-administration of lemborexant with weak inhibitors is predicted to produce exposure increases of less than twofold. Thus, simulations presented in this work support the recommendation that the dose of lemborexant should be no greater than 5 mg when the drug is co-administered with weak CYP3A inhibitors.

CONCLUSION

The developed model reconstructed to a high degree the observed PK profiles of lemborexant after multiple dosing of lemborexant alone, and after single dosing of lemborexant in combination with CYP3A inhibitors. This suggests that this validated model is a useful tool for predicting lemborexant exposure and DDIs with CYP3A inhibitors in lieu of clinical trials. The results suggest that co-administration of lemborexant with strong and moderate CYP3A inhibitors should be either avoided or lemborexant should not exceed 2.5-mg doses (in countries where 2.5 mg is approved). In patients receiving weak CYP3A inhibitors, a dose maximum of 5 mg should maintain the safety profile of therapeutic doses of lemborexant.

CONFLICT OF INTEREST

T.U. and Y.M. are employees of Eisai Co. Ltd., Japan. I.L., B.L., and E.S. are employees of Eisai Inc., USA.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

DATA AVAILABILITY STATEMENT

De-identified participant data that underlie the results reported in this article will not be made available, but summary information from the individual clinical trials used to generate this model will be made available on ClinicalTrials.gov.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.