

Population Pharmacokinetics of Lemborexant, an Orexin Receptor Antagonist, in Healthy Adult and Elderly Subjects and Subjects With Primary Insomnia

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Introduction

- Orexin neuropeptides (orexin-A and orexin-B) have been recognized as critical upstream controllers of most wake-promoting neurotransmitters via 2 G-protein–coupled receptors, the orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R). OX2R has been considered to be of higher importance for sleep-wake regulation than OX1R.¹⁻³
- Lemborexant (E2006) is a dual orexin receptor antagonist.⁴ These agents are hypothesized to be more effective for sleep promotion than antagonists for either receptor alone.⁵
- This analysis characterizes lemborexant pharmacokinetics (PK) and quantifies the effects of intrinsic and extrinsic factors in healthy adult subjects, elderly subjects, and subjects with insomnia disorder.

Methods

- This population PK analysis was based on 6 extensively sampled phase 1, 3 sparsely sampled phase 1, 1 sparsely sampled phase 2, and 2 sparsely sampled phase 3 studies (**Table 1**). Analysis was performed using nonlinear mixed-effect modeling in NONMEM® version 7.3. SAEM/IMP estimation under MPI parallelization enabled the analysis of this large pooled PK dataset, not readily feasible using the conventional estimation approach (FOCEI).
- A 3-compartment PK model, with mixed zero and first-order absorption with a lag-time and linear elimination from central compartment, was initially fit to data from the 6 extensively sampled phase 1 studies. Effects of dose, time of dosing (bedtime vs morning), formulation (tablet vs capsule), and food intake were evaluated as covariates for their effect on absorption parameters and relative bioavailability.
- The model was subsequently fit to all data (pooling extensively and sparsely sampled studies) with absorption parameters, relative bioavailability, and covariate effects on absorption and relative bioavailability fixed to those of the final PK model based on data from extensively sampled phase 1 studies.
- The pooled data model also evaluated covariates on apparent clearance (CL/F): body weight, age, sex, body mass index (BMI), race, creatinine clearance, laboratory parameters, concomitant medications (eg, gastric pH modifiers), and disease characteristics (insomnia vs healthy subjects).
- The population PK models under consideration were evaluated for performance using goodness-of-fit plots, visual predictive checks (VPCs), and nonparametric bootstrap.
- Ranges of lemborexant exposures were simulated across subpopulations of clinical interest assuming 5-mg bedtime steady-state dosing. Comparisons of 90% confidence intervals (CIs) for the difference in exposure [log(AUCss)] focused on (A) elderly subjects (≥ 65 years) and adult subjects (< 65 years, as a reference), and (B) underweight (median BMI = 17.4 kg/m²), overweight (median BMI = 27.4 kg/m²), and obese (median BMI = 32.7 kg/m²) subjects vs normal subjects (median BMI = 22.9 kg/m²).

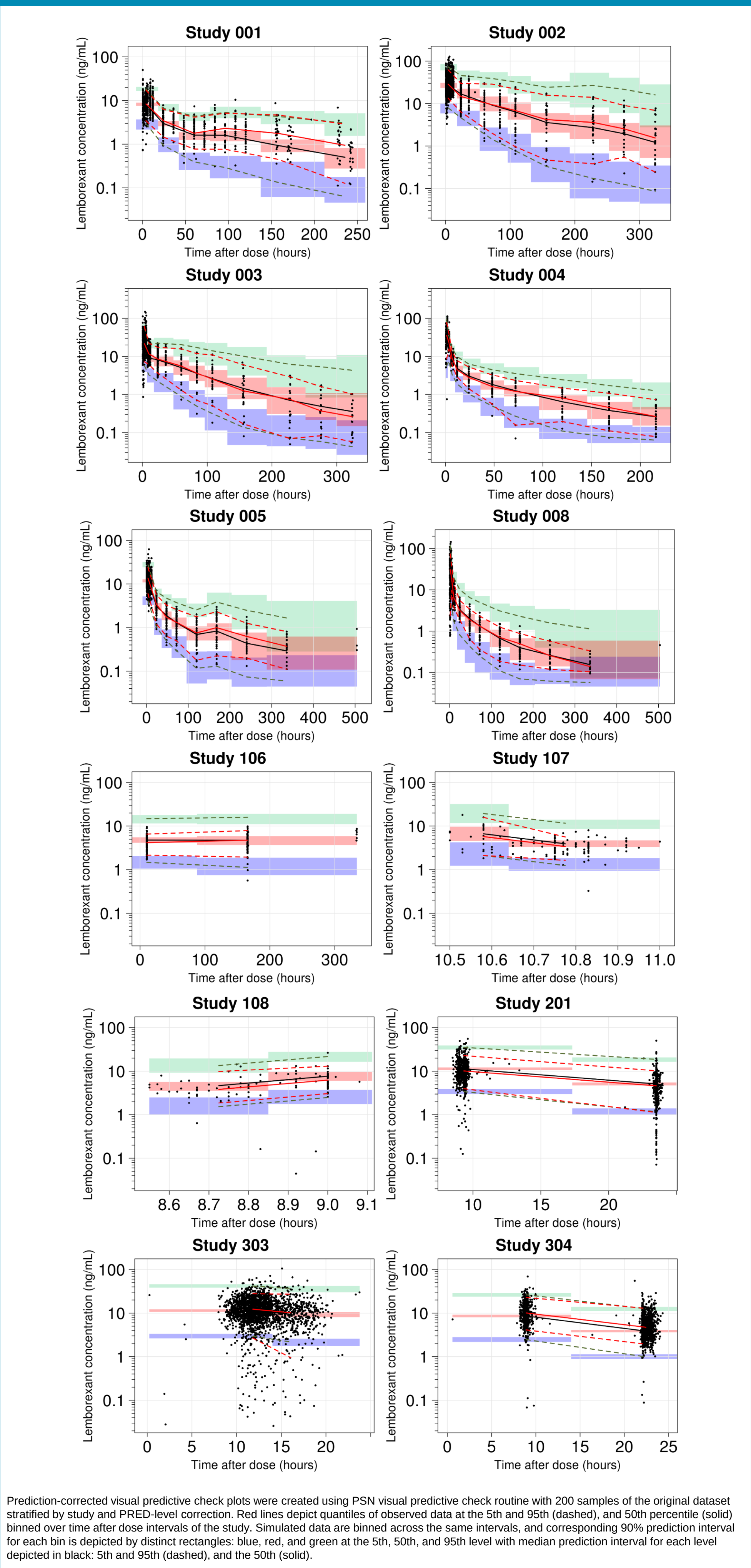
Table 1. Lemborexant Studies Included in the Population PK Analysis

Protocol Number	Study Design	Dose and Formulation	Number of Subjects in Dataset
Study 001	A 2-part, randomized, double-blind, placebo- and active-controlled, single-dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of E2006 in healthy subjects and otherwise healthy subjects with primary insomnia	Part A: placebo, 1, 2.5, 5, 10, 25, 50, 100, and 200 mg Part B: placebo, 2.5, 10, 25 mg and zolpidem 10 mg (capsule)	83
Study 002	A randomized, double-blind, placebo-controlled, multiple-ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of E2006 in healthy adult and elderly subjects	Part A (adult cohorts): placebo, 2.5, 5, 10, 25, 50, and 75 mg Part B (elderly cohort): placebo and 25 mg (capsule)	41
Study 003	A 2-part, randomized, double-blind, placebo-controlled, multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of E2006 in healthy Japanese and white subjects	Part A: placebo, 2.5, 10, and 25 mg Part B: placebo and 10 mg (tablet)	24
Study 004	A 2-part, open-label study to assess potential metabolism-based drug-drug interactions of E2006 when co-administered with itraconazole (CYP3A inhibitor), rifampin (CYP3A inducer), midazolam (CYP3A substrate), or bupropion (CYP2B6 substrate)	10-mg tablet	30
Study 005	A single-center, open-label, randomized, multi-cohort, crossover study of relative bioavailability of tablet vs capsule formulation of E2006 in healthy adult subjects	2.5-, 10-, and 25-mg capsule and tablet	40
Study 008	An open-label, single-dose, randomized crossover study to determine the effect of a high-fat meal on the rate and extent of E2006 absorption in healthy subjects	10-mg tablet	24
Study 106	A randomized, double-blind, placebo- and active-controlled, 4-period crossover study to evaluate the effect of lemborexant vs placebo on driving performance in healthy adult and elderly subjects	2.5-, 5-, and 10-mg tablet	48
Study 107	A randomized, double-blind, placebo-controlled, 3-way crossover study to evaluate the effect of 2 dosage strengths of E2006 on a multiple sleep latency test in subjects with insomnia disorder	5- and 10-mg tablet	63
Study 108	A randomized, double-blind, placebo-controlled and active-comparator, 4-period crossover study to evaluate the effect of lemborexant vs placebo and zolpidem on postural stability, auditory awakening threshold, and cognitive performance in healthy subjects 55 years and older	5- and 10-mg tablet	60
Study 201	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, Bayesian adaptive randomization design, dose-response study of the efficacy of E2006 in adults and elderly subjects with chronic insomnia	1, 2.5-, 5-, 10-, 15-, and 25-mg tablet	235
Study 303	A long-term multicenter, randomized, double-blind, controlled, parallel-group study of the safety and efficacy of lemborexant in subjects with insomnia disorder	5- and 10-mg tablet	726
Study 304	A multicenter, randomized, double-blind, placebo-controlled, active comparator, parallel-group study of the efficacy and safety of lemborexant in subjects 55 years and older with insomnia disorder	5- and 10-mg tablet	524

Table 2. Lemborexant Population Pharmacokinetics Dataset Demographics			
All Subjects (N = 1892)			
Covariate, unit	Mean (SD)	Median	Range (min-max)
Age, y	55 (14.1)	57	18-88
Age by group	Adults n = 1345; Elderly (≥ 65 y) n = 547		
Weight, kg	75.5 (15.7)	74.1	37-168
BMI, kg/m ²	27.0 (5.0)	26.5	14.4-62.1
BMI by category	Underweight n = 27; Normal n = 650; Overweight n = 804; Obese n = 411		
Bilirubin, μmol/L ^a	6.9 (4.1)	6.0	1.7-42.9
Albumin, mg/dL ^b	44.2 (2.8)	44	26-53
Alanine transaminase, IU/L ^b	20 (11.9)	17	5-178
Aspartate transaminase, IU/L ^b	20.7 (8.3)	19	8-194
Alkaline phosphatase, IU/L	72.9 (22.0)	71	13-256
Creatinine clearance, mL/min ^b	101.7 (35.1)	97.3	26.8-319
Dose, mg	Range: 1-100		
Sex	Female = 1249, Male = 643		
Race	White = 1334; Black/African American = 335; Asian/Other Asian (excluding Chinese and Japanese) = 32; Japanese = 155; Chinese = 5; American Indian/Alaskan/Other/Missing = 31		
Formulation	Tablet = 1755, Capsule = 137		
Concomitant PPI	Yes = 112, No = 1780		
Concomitant CYP3A	Yes = 22, No = 1870		
^a n = 1888; ^b n = 1891.			
BMI, body mass index; PPI, proton pump inhibitor; PK, pharmacokinetics; SD, standard deviation.			

Table 3. Lemborexant Population PK Parameters			
Parameter	Point Estimate	%RSE	95% CI (Bootstrap CI)
CL/F			
Typical value CL/F, L/h	22.7	0.252	22.6-22.8 (22.6-23.6)
Effect of BMI on CL/F, exponent	-0.428	12.9	-0.536 to -0.320 (-0.484 to -0.249)
Effect of ALP on CL/F, exponent	-0.118	21.3	-0.167 to -0.069 (-0.269 to -0.144)
Effect of Elderly on CL/F, ratio	0.739	0.307	0.735-0.753 (0.688-0.749)
V2/F			
Typical value V2/F, L	9.09	0.0909	9.07-9.11 (8.1-13.7)
Q3/F			
Typical value Q3/F, L/h	32.1	0.0417	32.1-31.1 (32.2-37.55)
V3/F			
Typical value V3/F, L	278	0.0156	278-278 (244-314)
Q4/F			
Typical value Q4/F, L/h	31.0	0.0997	30.9-31.1 (25.1-31.0)
V4/F			
Typical value V4/F, L	783	0.0815	782-784 (729-820)
D1			
D1 for capsule, h	0.467	Fixed	
D1 tablet effect, ratio	0.254	Fixed	
D1 bedtime dosing effect, ratio	2.33	Fixed	
Ka, 1/h			
Ka for capsule, 1/h	0.532	Fixed	
Ka tablet effect, ratio	1.12	Fixed	
Ka effect of food, ratio	0.695	Fixed	
ALAG1, h	0.403	Fixed	
Relative bioavailability			
F1 fed	1.21	Fixed	
Inter-individual variability, %CV			
CL/F	48.1	3.68	(44.9-49.5)
V2/F	142	23.2	(78.1-140)
Q3/F	56.8	17.2	(25.5-47.3)
V3/F	82.0	15.0	(63.1-76.9)
Q4/F	46.5	11.4	(18.5-50.6)
V4/F	41.4	10.5	(30.1-41.1)
D1	167	Fixed	
Ka	43.8	Fixed	
F1	68.1	Fixed	
Residual variability			
Proportional (TAD > 3 h), %CV	14.3	1.07	(13.5-15.1)
Additive (TAD > 3 h), ng/mL	0.0189	21.2	(0.014-0.027)
Proportional (TAD ≤ 3 h), %CV	32.9	1.19	(31.9-34.3)
Additive (TAD ≤ 3 h), ng/mL	2.62	3.15	(0.99-4.40)
ALAG1, lag time in absorption; ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; CL/F, apparent clearance; %CV, square root of variance * 100; D1, duration of absorption; Ka, first-order absorption rate constant; PK, pharmacokinetics; Q/F, inter-compartment clearance; %RSE, percent relative standard error of the estimate = SE/parameter estimate * 100; TAD, time after dose; V2/F, apparent central volume of distribution; V3/F, apparent first peripheral volume of distribution; V4/F, apparent second peripheral volume of distribution.			

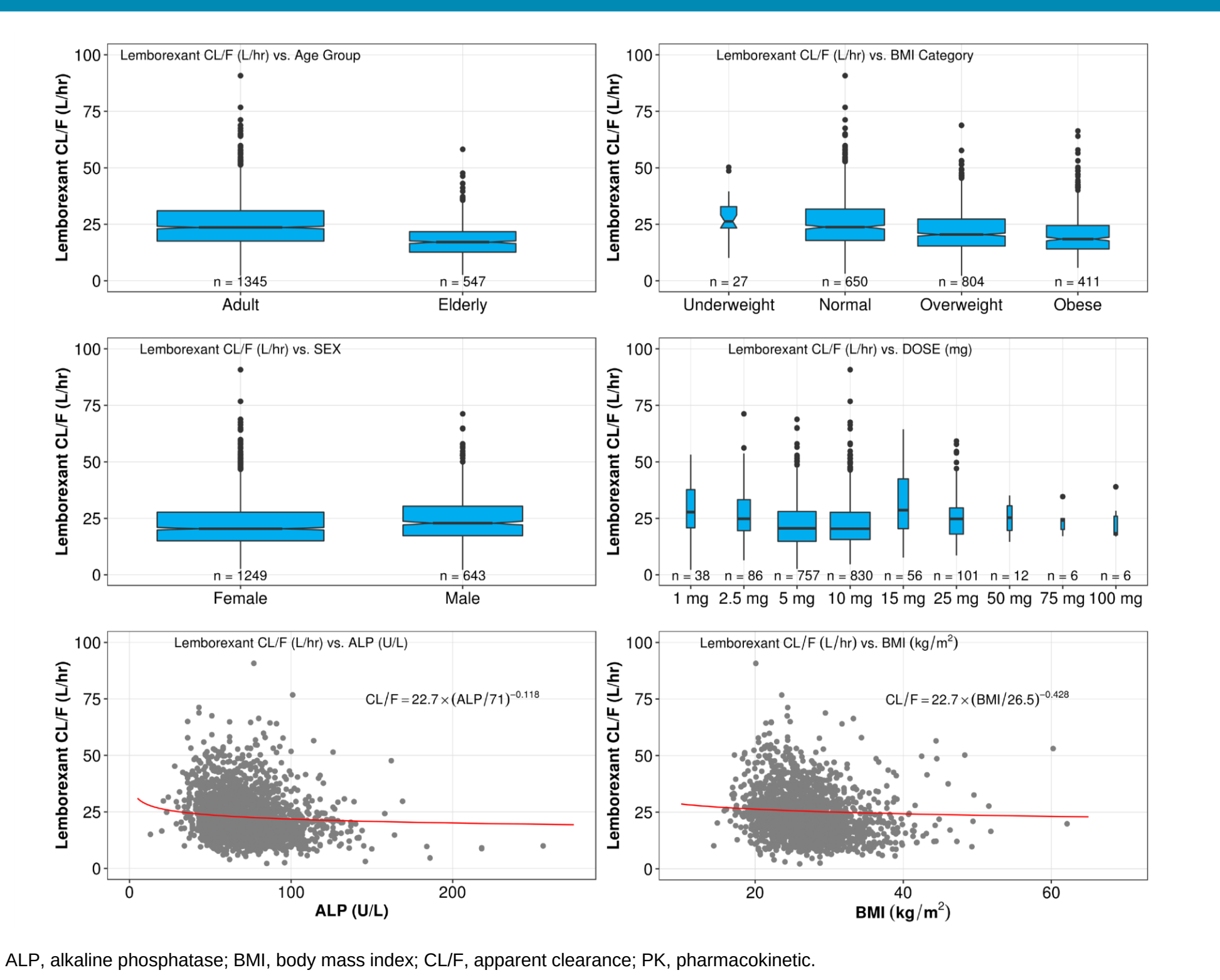
Figure 1. Lemborexant Population Pharmacokinetic Prediction-Corrected Visual Predictive Check Plots Stratified by Study



Results

- The PK dataset included 12,230 observations from 1892 subjects: aged 18-88 years weighing 37-168 kg and predominantly female (66%) and white (70%). A summary of the demographics for PK population is presented in **Table 2**.
- Lemborexant PK was best described by a linear 3-compartment model with mixed zero (D1) and first-order (Ka) absorption with lag-time. Linear elimination from the central compartment was assumed. The model included a combined (additive/proportional) residual error with distinct parameters for lemborexant sampling times before and after 3 hours postdosing.
- The base PK model based on phase 1 studies incorporated absorption-related significant covariate effects: bedtime dosing on D1, effect of food on Ka and relative bioavailability (F1), and effect of formulation on D1 and Ka. For the tablet formulation, D1 was 0.118 hours with bedtime dosing increasing D1 by 2.33-fold; Ka was estimated to be 0.595 (1/h). The effect of food decreased Ka by 30% while increasing F1 by 21% (**Table 3**).
- Due to the absence of PK sampling in the first 9 hours following bedtime dosing for the 1 phase 2 and 2 phase 3 studies, the inclusion of covariates in the final model was constrained to the clearance parameter (CL). High eta (η) shrinkage (> 60%) was noted for all other between-subject variability parameters except CL.
- All VPCs illustrated very good concordance across the quantiles of predicted and observed data; prediction-corrected VPC plots are depicted in **Figure 1**. Bootstrap CIs were slightly wider than the asymptotically derived CIs, confirming robustness of final model parameter estimates (**Table 3**).
- With the final model, lemborexant CL/F decreased significantly with increasing BMI (exponential coefficient = -0.428), increasing alkaline phosphatase (ALP) levels (exponential coefficient = -0.118), and was 26% lower in the elderly subjects (≥ 65 years) (**Table 4** and **Figure 2**).

Figure 2. Lemborexant CL/F vs Population PK Model Covariates



ALP, alkaline phosphatase; BMI, body mass index; CL/F, apparent clearance; PK, pharmacokinetic.

Table 4. Comparison of Simulated Lemborexant AUCss for Elderly vs Adults and Across Categories of BMI

Dose	ln(AUCss)		Ratio (%)	Lower 90% CI	Upper 90% CI
	Test	Ref			
5 mg	Normal (BMI = 22.9 kg/m ²)	Underweight (BMI = 17.4 kg/m ²)	89	83	96
		Overweight (BMI = 27.4 kg/m ²)	111	103	119
		Obese (BMI = 32.7 kg/m ²)	119	111	128
5 mg	Elderly (≥ 65 y)	Adults	139	129	150

Comparisons were based on 250 representative subject re-samples. Lemborexant exposures (AUCss) assumed a 5-mg nightly dose at steady state, and population median BMI of 26.6 kg/m² and ALP of 71 IU/L. 90% CI for the difference in log(AUCss) of the test and reference formulations was used as a basis for comparison.

ALP, alkaline phosphatase; AUCss, area under the curve steady state; BMI, body mass index; CI, confidence interval.

Conclusions

- Lemborexant PK data in healthy subjects and subjects with insomnia disorder were described by a 3-compartment model with combined first- and zero-order absorption and linear elimination from the central compartment, and relative bioavailability (F1) for food intake.
- Statistically significant effects of tablet formulation and bedtime dosing on D1, tablet formulation and food intake on Ka, elderly age (categorical), BMI (continuous), and ALP (continuous) on CL/F and food intake with tablet formulation on F1 were identified. The effects of formulation (tablet vs capsule), food, and bedtime dosing were minor and of no clinical relevance.
- The effects of age category, BMI, and ALP were minimal and within the inter-individual variability range in CL/F. In the absence of a notable exposure-response for the most frequent phase 3 treatment-emergent adverse events, which included somnolence (data not presented), higher exposures are not considered to be of clinical relevance and do not warrant dose adjustment.
- Lemborexant CL/F was dose independent and not significantly affected by race, sex, body weight, creatinine clearance, liver enzymes (other than slight effect of ALP), or concomitant proton pump inhibitors.

References

- Akanmu MA, Honda K. *Brain Res*. 2005;1048:138-145.
- Dugovic C, et al. *J Pharmacol Exp Ther*. 2009;330:142-151.
- Hondo M, et al. *Acta Physiol*. 2010;198:287-294.
- Murphy P, et al. *J Clin Sleep Med*. 2017;13:1289-1299.
- Moraity SR, et al. *PLoS One*. 2012;7:e39131.

Disclosures

- BL, OM, ISL, LR, MM, JF, and ZH are employees of Eisai Inc.

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