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Population Pharmacokinetics and Exposure-Response Analyses for the Most Frequent Adverse Events Following Treatment With Lemborexant, an Orexin Receptor Antagonist, in Subjects With Insomnia Disorder

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Abstract

Lemborexant is a novel orexin receptor antagonist approved in the United States and Japan for the treatment of insomnia. This article describes the population pharmacokinetics (PK) of lemborexant and the relationship of its daily steady-state exposure ($C_{av,ss}$) to the probability of most frequent treatment-emergent adverse events (TEAEs). The 12 230-observation, 1892-subject PK data set included data from 12 clinical studies with predominantly female subjects (66%) ranging in age from 18 to 88 years and from 37 to 168 kg in body weight. The 1664-subject exposure-response data set included data from 3 late-stage studies. Lemborexant pharmacokinetics were described by a 3-compartment model with combined first- and zero-order absorption with lag time and linear elimination. Oral clearance decreased with increasing body mass index (exponent, −0.428), increasing alkaline phosphatase levels (exponent, −0.118), and was 26% lower in the elderly (≥65 years). Across the adverse event analysis, the frequency of subjects experiencing TEAEs during active treatment ranged from approximately 3% to 8%, in the range estimated for placebo. With and without adjustment for age, lemborexant exposure ($C_{av,ss}$) was not a clinically meaningful linear predictor of the probability of specific TEAEs: somnolence, nasopharyngitis, flu/influenza, urinary tract infection, upper respiratory tract infection, or headache. Given the small effect sizes of covariates of the PK model and a low degree of association of lemborexant TEAEs and exposure over the range of phase 3 (therapeutic) 5- and 10-mg doses, lemborexant can be safely administered without the need for dose adjustment.

Keywords

exposure-response analysis, insomnia, orexin antagonist, population pharmacokinetics

The prevalence of insomnia is high, with up to two-thirds of the general population reporting difficulty initiating or maintaining sleep and waking up too early with nonrestorative or poor sleep quality. Approximately 10% to 15% of ambulatory patients and generally healthy subjects report chronic insomnia with daytime consequences.[1-4] Insomnia and daytime sleepiness are associated with depression, with insomnia and other sleep disturbances considered precursors and predictors of depressive disorders, raising the question if early, adequate treatment of insomnia may alleviate its psychiatric sequelae.[5,6] The resulting high economic impact and cost of insomnia are well established.[7] Physiological changes associated with aging and chronic illnesses contribute to insomnia in the elderly, in whom this condition is more prevalent, as sleep patterns change with age.[8-12]

Most currently approved insomnia therapeutics act via modulation of G-protein-coupled receptors distributed across specific areas of the brain, which in turn affect different sleep characteristics. Benzodiazepines and nonbenzodiazepine hypnotics (Z-drugs) are positive allosteric modulators at the gamma aminobutyric acid A (GABA$_A$) receptor, potentiating the effects of the GABA neurotransmitter and therefore attenuating neuronal activity.[13] The main difference between benzodiazepines and Z-drugs involves their receptor affinities

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across different GABA$_A$ subunits, with Z-drugs exhibiting higher affinity for a subset of the alpha GABA$_A$ subunits (α1). Z-drugs have been noted to have considerable therapeutic liabilities, including dizziness, ataxia, memory disturbances, and sleep-related behaviors that carry over into the day, impairing functioning. These drugs act predominantly as hypnotics and sedatives and require a short duration of action (rapidly declining exposures and short half-lives) to minimize residual daytime sedative effects. Consequently, this constrains the effectiveness of these agents throughout the full sleep period. This issue has gathered considerable attention from the United States Food and Drug Administration (FDA) and other regulatory agencies.[14,15] Melatonergics, developed over the last 20 years, have similarly demonstrated a generally limited efficacy.[13] Agomelatine, a melatonin analogue initially evaluated for its body clock phase adjustment and antidepressant properties, is currently approved only in the European Union. Prolonged-release melatonin has shown efficacy in the treatment of insomnia disorder in adults older than 55 years of age, based on 4 randomized, controlled trials, whereas a melatonin agonist, ramelteon, has shown benefit in sleep-onset insomnia, but not for the treatment of maintenance insomnia because of its short duration of action.

Orexin receptor antagonists represent a more recent approach to treatment of insomnia. 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 of higher importance for sleep-wake regulation than OX1R.[16-18] Dual-receptor antagonists are hypothesized to be more effective for sleep promotion than antagonists for either receptor alone.[19] Suvorexant (Belsomra, Merck & Co., Kenilworth, New Jersey) was the initial orexin receptor antagonist approved by the FDA for the treatment of insomnia in adults and elderly over 12 months of treatment with doses of 5-20 mg nightly. Lemborexant, a dual-receptor antagonist, has been studied in 22 clinical studies and has been recently approved by the US FDA and the Japanese Ministry of Health, Labor and Welfare. Of note, 2 phase 3 studies, SUNRISE 1 and SUNRISE 2, included approximately 2000 adults with insomnia and assessed lemborexant versus active comparator for as long as 1 month and versus placebo for 6 months.[20,21]

The pharmacologic approach of orexin receptor antagonism allows for a reconsideration of pharmacokinetic (PK) properties of an effective agent. It may be conceptualized that the ideal PK characteristics of an orexin antagonist would support both an initially rapid concentration rise to promote onset and sustained concentrations during the sleep period (sleep maintenance), that is, OXR antagonism during the night would attenuate endogenous OXR central nervous system ligand (hypocretin/orexin) concentrations. In the morning, the potential impact of residual daytime drug concentrations would be countered by a rise of hypocretin/orexin, which is under diurnal control. Clinically, morning residual effects such as somnolence would be under the control of both increasing concentrations of orexin and rapidly decreasing antagonist concentrations during its elimination phase.[22,23]

To that end, the characterization of PK of an insomnia therapeutic, the quantification of its variability, and the effect of its covariates represent a key step in the evaluation of its appropriate dose and dosing regimen. This article describes the development of a model of lemborexant population PK across studies of its clinical development program to describe the PK and to quantify the effects of intrinsic and extrinsic factors in healthy adults, the elderly, and subjects with insomnia disorder. Given that the incidence of insomnia increases with aging, it was of particular interest to establish if the elderly experience changes in lemborexant exposure that could result in differential safety or therapeutic efficacy responses to lemborexant. An exposure-response model-based analysis was undertaken to delineate the relationship of lemborexant exposure and treatment-emergent adverse events (TEAEs) across 3 late-stage studies.

Methods

Bioanalysis

Blood samples (4 mL each) were collected for the assessment of lemborexant PK, with sampling times for each study presented in Supplemental Table 1. Lemborexant concentrations in plasma were determined by liquid-liquid extraction followed by analyte quantification using reverse-phase high-performance liquid chromatography-mass spectrometry (AB Sciex API 4000, SCIEX, Concord, Ontario, Canada) operated under multiple reaction monitoring-positive ion mode. The assay monitored mass-to-charge ratio (m/z) 411.0 → 287.1 for lemborexant and 414.0 → 290.1 for the deuterated internal standard. The lower limit of quantification of the assay and its linear calibration range were 0.05 and 0.05-50.0 ng/mL, respectively, with appropriate bioanalytical noninterference of coadministered compounds demonstrated before sample analysis. The validated method had an interday and intraday precision and accuracy (bias) of less than 12%, with incurred sample reanalysis passing the criteria in each individual study. Successful cross-validation was established across 2 bioanalytical laboratories that handled all sample analyses.

Population Pharmacokinetic Model Development

This analysis used a nonlinear mixed-effects modeling approach using NONMEM version 7.3.[24] R and Perl-speaks-NONMEM (PsN) were used for model evaluation and model goodness-of-fit diagnostics to generate visual predictive check (VPC) simulations and bootstrap replicates to obtain bootstrap standard errors of model parameter estimate.[24,25] The analysis of extensively sampled PK data (phase 1 studies) employed a first-order estimation method conditional on the interindividual and residual variability (η-ε) interaction (FOCEI). For the larger data set (final model, see below), FOCEI followed by stochastic approximation-estimation and importance sampling estimation methods was used. This estimation method allowed the model to achieve convergence and completion of the covariance estimation with an objective function value (OFV) appropriate for likelihood testing.[26] This sequence of estimation steps under message passing interface parallelization enabled the analysis of a large pooled PK data set, not readily feasible using the conventional FOCEI estimation approach.

The OFV was considered a key goodness-of-fit statistic and the difference in the objective function value (ΔOFV; -2 log likelihood) of nested models was assumed to asymptotically follow a chi-square distribution, with the degrees of freedom equal to the difference in the number of parameters between 2 nested models. As part of this analysis, the larger nested model was retained if the ΔOFV exceeded the $P < .01$ significance level. In contrast, for nonnested models, the parsimonious approach was applied; the model with the fewest parameters and the lower ΔOFV adequately describing the data was selected with no a priori ΔOFV (-2LL) cutoff assumed. The structural models under initial consideration were 2- or 3-compartment models with first-, zero-, or mixed-order absorption. Individual-level PK parameters were assumed to be lognormally distributed and were parameterized conventionally (within reference equation 5).[27,28] The differences between observed and model-predicted individual concentrations (residual error) were assumed to be either proportional or related to the predicted concentrations via a combination of additive and proportional terms and could be conditional on covariates or study design factors.[27] Base model covariates, initially noted to influence lemborexant PK (the effects of coadministration with food [standard high-fat meal], tablet versus capsule formulation, bedtime dosing, insomnia, and healthy subjects) were initially incorporated using the full-model approach (see Base Model section in Results).[29,30] Other covariates of interest were examined as part of the final model analyses, using a stepwise approach, with forward addition and backward elimination.[24]

The effects of other subject-level, time-invariant covariates included demographics (age, body weight, body mass index [BMI], sex, race designation), laboratory values at baseline (serum albumin [ALB], aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], total bilirubin, and estimated baseline creatinine clearance [CrCL]). Age, body weight, and BMI were explored as either a continuous or a categorical covariate (elderly and adults) or lightweight, normal, heavyweight, or obese (per standard Centers for Disease Control and Prevention categories). The impact of lemborexant administration with concomitant proton pump inhibitors (PPIs) was also assessed. Covariates were included multiplicatively on PK parameters of interest.[27]

Model Evaluation

Models were evaluated considering successful convergence of the estimation procedure, plausibility, collinearity, and distribution of model parameters employing diagnostic plots, VPC procedures, and bootstrap analyses. Two hundred fifty simulated replicates of the observed data set were generated using the PsN VPC utility, overlaying key observed and simulated quantiles, the median and 5th and 95th percentiles, and depicted the 95% confidence intervals (CIs) of the simulation replicates.[24,28] Using the PsN bootstrap procedure, 1000 nonparametric replicate data sets with replacement were generated based on the original data with models fitted to each of these replicated data sets.

Analysis of Exposure-Response of Treatment-Emergent Adverse Events

Lemborexant exposure (average steady-state concentration [$C_{av,ss}$]), age, sex, and race were considered explanatory variables of a generalized linear model (GLM) with a logit link function describing the probability of a subject experiencing a TEAE at any time, using the GLMs package in R.[25,30] TEAEs considered for this analysis were those events arising in more than 30 subjects across the single phase 2 and 2 phase 3 studies (E2006-G000-202, E2006-G000-303, and E2006-G000-304) at the incidence rate of approximately >3% (Supplemental Table S1). The model assumed a linear relationship log odds of experiencing a TEAE and lemborexant $C_{av,ss}$ and other covariates of the model as linear predictors of the adverse event logit, primarily because of the range of lemborexant exposures across the studies. Placebo treatment data were also included to afford a comparison. Race designation was categorized as white, black/African American, Japanese, and "others."
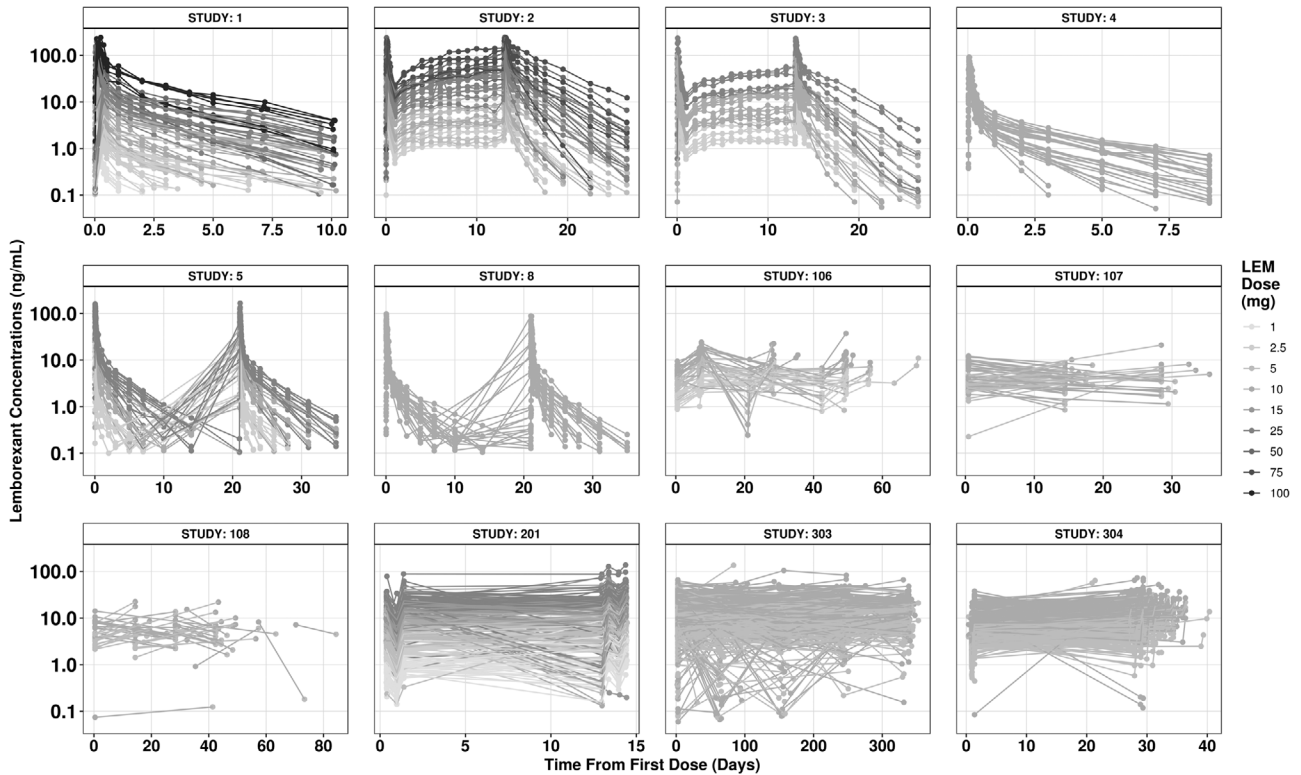
Figure 1. Observed lemborexant concentration-time data for each study used in the population pharmacokinetic analysis, with time in days from first lemborexant dose for each study (top, A) or with time in days after first lemborexant dose for each study (Supplemental Figure S1; B).

Results

Lemborexant PK Data and Demographics
The population PK analysis was based on data from 6 extensively and 3 sparsely sampled phase 1 studies, 1 sparsely sampled phase 2 study, and 2 sparsely sampled phase 3 studies (Supplemental Table S1). The population PK data set consisted of 12 230 observations from 1892 subjects with at least 1 dose and a single lemborexant concentration measurement (Figure 1 and Supplemental Figure S1). Supplemental Table S1 also lists the information pertaining to the 12 studies making up the PK data set. Phase 1 studies contributed 6543 observations from 407 subjects. Phases 2 and 3 studies contributed 5687 observations from 1485 subjects, with the 2 phase 3 studies (303 and 304) contributing 2211 and 1972 lemborexant plasma concentrations, respectively, from 726 and 524 subjects, respectively. Subjects included in this analysis were 18-88 years old, with body weight ranging from 37 to 168 kg and were predominantly female (66%) and white (70%). Table 1 presents baseline demographic characteristics and baseline liver and renal function tests (ALT, ALP, bilirubin, AST, ALB, and CrCL) of the subjects of the PK data set. In addition, the data set included drug formulation (tablet or capsule), information about administration in the fed or fasted state, daytime or bedtime dosing, study

participants (healthy or insomnia subjects), and any use of PPIs and moderate or strong concomitant CYP3A medication at baseline.

Population PK Model

Base Model. A 3-compartment model (Supplemental Figure S2) with linear elimination from the central compartment and a mixed first-order (K_a) and zero-order (D1) absorption with a lag time (ALAG1) was superior to an alternative 2-compartment model initially used to describe lemborexant PK data from 6 extensively sampled lemborexant studies (Supplemental Table S1; studies 001, 002, 003, 004, 005, and 008).

Mixed, first-, and zero-order absorption was superior in terms of both objective function and goodness-of-fit plots to models describing the absorption using either zero- or first-order processes alone. Models were parameterized in terms of clearance and volume of distribution parameters (ADVAN12, TRANS 4) with a residual variability modeled using an additive and a proportional parameter using the NONMEM FOCEI estimation method with the covariance estimation step. A modified sequence of FOCEI estimation followed by SAEM and Monte Carlo IMP (the latter estimation step used to obtain a reliable objective function estimate) provided consistent estimation of standard

Table 1. Summary of Covariates for the Population PK Analysis of Lemborexant (n = 1892)

Covariate	Mean (SD)	Median	Range (Min-Max)
Age (years)	55 (14.1)	57	18-88
Weight (kg)	75.5 (15.7)	74.1	37-168
BMI (kg/m^2)	27.0 (5.0)	26.5	14.4-62.1
Bilirubin (mg/dL)	0.40 (0.23)	0.35	0.10-2.5
μmol/L[a]	6.9 (4.1)	6.0	1.7-42.9
Albumin (g/dL)	4.42 (0.28)	4.4	2.6-5.3
g/L[b]	44.2 (2.8)	44	26-53
Alanine transaminase (U/L)[b]	20 (11.9)	17	5-178
Aspartate transaminase (U/L)[b]	20.7 (8.3)	19	8-194
Alkaline phosphatase (U/L)	72.9 (22.0)	71	13-256
Creatinine clearance (mL/min)[b]	101.7 (35.1)	97.3	26.8-319
Age categories[d]	Adults, 1345		
	Elderly ($\geq$65 years), 547		
BMI categories[c,d]	Underweight (BMI < 18.5 kg/m^2), 27		
	Normal (BMI 18.5-24.9 kg/m^2), 650		
	Overweight (BMI, 25-29.9 kg/m^2), 804		
	Obese (BMI >30 kg/m^2), 411		
Dose[d]	Range, 1-100 mg		
Sex[d]	Women, 1249		
	Men, 643		
Race[d]	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[d]	Tablet, 1755		
	Capsule, 137		
Concomitant PPI[d]	Yes = 112		
	No = 1780		
Weak concomitant CYP3A inhibitors[d]	Yes, 22		
	No, 1870		

BMI, body mass index; PPI, proton pump inhibitor; SD, standard deviation.
[a]n = 1891.
[b]n = 1888.
[c]Adapted from https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf.
[d]Values depict number of subjects.

errors and faster convergence over FOCEI with co-variance. The SAEM estimation options (CTYPE = 1, ISAMPLE = 2, NBURN = 3000, NITER = 750) were maintained throughout the subsequent modeling steps. This estimation was followed by importance sampling (EONLY = 1, NITER = 25, ISAMPLE = 10000, IACCEPT = 1, MAPITER = 0) to obtain the maximum likelihood estimates for each NONMEM run. For this modeling step, intersubject variability was estimated for all parameters except for ALAG1 with combined additive and proportional residual error terms for concentrations up to 3 hours after dosing and an additional, distinct term for concentrations measured after 3 hours following dosing, which reflected the general cutoff time of the data arising from extensively sampled healthy-subject studies, conducted in an inpatient setting. This residual error modification resulted in a highly significant reduction in the OFV value compared with a model with an additive/proportional combined residual variability. The effect of administration with food, tablet versus capsule formulation, and bedtime dosing were initially noted as important factors influencing lemborexant absorption processes and PK using noncompartmental approaches.[31]

These covariate effects were initially examined univariately on D1 and K_a parameters, resulting in high objective function decreases ($P < .001$) to form the base model. The model incorporated the effect of tablet formulation, bedtime dosing, and a dose adjustment factor for doses $\geq$ 50 mg on D1, accounting for small deviations from dose-proportionality of high lemborexant doses (which were not considered in phase 2/3 studies). Tablet formulation and food intake were included covariates on the first-order absorption parameter (K_a); lemborexant coadministration with food increased the estimate of relative bioavailability (F1) by 21%. Zero-order absorption duration for the tablet formulation was approximately 0.118 hours compared with 0.467 hours for the capsule, with bedtime dosing resulting in a 2.33-fold increase in D1 and tablet

formulation resulting in a 12% increase in K_a; dosing with food intake decreased K_a by 30%. The effects of tablet formulation and bedtime dosing on D1 and tablet formulation and food on K_a and F1 were fixed for subsequent final-model lemborexant analysis that was extended to include sparsely sampled individual PK data from phases 2 and 3 studies. The base model (Supplemental Table S2) exhibited an eigenvalue ratio of approximately 200 and generally low standard errors of estimates. Specifically, the model parameter displayed a percent relative standard error (% RSE) < 20%, except for the effect of dose ≥ 50 mg on D1 (% RSE, 42.5). Shrinkage of random-effect parameter on clearance did not exceed 20%.

Final Model. The analysis was extended to all available PK data from phases 1, 2, and 3 studies (Table 1) with 6 additional sparsely sampled phase 1 studies (106, 107, and 108), 1 phase 2 study (201), and 2 phase 3 studies (303 and 304). Common to these studies is a general absence of lemborexant PK sampling over the first 7-9 hours following bedtime dosing (ie, the data during the absorption and initial elimination phase; Figure 1, Supplemental Figure S1, Table 1). Several steps were taken to examine the impact of simplification of several structural aspects of the base model in the presence of all available data. These included an evaluation of a separate residual error term for the cohort of sparse sampling studies, parameter estimation in the presence of fixed parameters for K_a, D1, and ALAG1, and the impact of removal of a parameter estimating an offset in D1 for doses ≥ 50 mg once daily. Inclusion of these simplifications resulted in negligible fit deterioration while improving full-model stability (Table 2).

Covariate analyses were conducted with a focus on estimation of oral clearance (CL/F) as a PK measure reflecting daily exposure ($C_{av,ss}$) for use in subsequent longitudinal exposure-response analyses. It was noted that the initial PK models reflected to a large extent eta (η) shrinkage (>60%) for all between-subject variability parameters except clearance (11.7%), and final model covariates were parameterized as regressors of the NONMEM CL parameter. Demographic factors, age, race, body weight, and size (BMI), were a priori established key covariates of clinical interest. Markers of renal function (CrCL) and hepatic function (AST, ALT, ALP, bilirubin, and ALB) and PPI use were also included as part of univariate analyses ($P < .01$). As part of the univariate forward-addition testing procedure, age was considered as either a continuous covariate or as a categorical covariate on CL/F for elderly (defined as >65 years old), versus adults, and resulted in a statistically significant change of the objective function, with a similar small effect size (126%). The categorical covariate for age was used subsequently. The additional statistically significant forward addition covariates in the full model were the effects of ALP, BMI, and concomitant PPIs on clearance (Table 2). Backward elimination ($P < .001$) of PPIs did not retain this covariate, whereas ALP, BMI, and elderly were retained in the final model. In addition to the effect of decreased CL/F in the elderly (covariates on clearance), CL/F was found to decrease with increasing BMI (power relationship exponent, −0.428) and increasing ALP (power relationship exponent, −0.118). A weak correlation ($r^2 < 0.05$) was noted across final lemborexant model covariates.

Goodness-of-Fit and Model Performance. This PK model indicated a general independence of residuals with respect to time and typical subject prediction and individual-level prediction irrespective of sparse or extensive PK sampling study design (Supplemental Figure S3). Final model parameters presented in Table 2 include nonparametric bootstrap estimates, which indicates general stability and consistency of parameter estimates of the final model. The bootstrap estimates were based on 250 replicate data sets, with s 93% success rate with 1 run failing to terminate. Fifteen runs with terminated minimization were skipped for the bootstrap summary. The final study-stratified PK model VPC plots are presented in Figure 2 based on 250 replicates of the analysis data set under the automatic PsN binning option. The plots indicate an adequate predictive performance of the final model, illustrating a general concordance of simulated and observed study-stratified data across time and all quantiles of PK data.

Clinically Relevant Covariates of the Lemborexant Population PK Model. Covariate effects of the final model are depicted in Figure 3. The box plots illustrate the relationship of individual predictions of clearance versus categorized age (adult versus elderly > 65 year old), BMI, and ALP, with all covariates illustrating a decreasing trend in clearance (increasing exposure). Relative to the population average, the model predicts 26% higher exposures in the elderly, 9% higher exposures for high (150 U/L) ALP, and 9% lower exposures for low ALP (35 U/L). Relative to the typical subject CL/F value with a normal BMI, only slightly higher CL/F effect sizes were noted for BMI of 15 kg/m² (underweight), predicted to result in 25% lower exposures. Higher exposure of 11% was predicted for a BMI of 32 kg/m² (class 1 obesity).[32] For BMI 40 kg/m² (morbid obesity), the effect was predicted to result in 22% higher exposures, a higher end of patient BMIs across the studies. The effects of sex, race, and dose were of clinical interest but did not enter

Table 2. Lemborexant Population PK Parameters

Fixed-Effects Parameter	Estimate	% RSE	95% Asymptotic CI[a]	Bootstrap Median	95% Bootstrap CI[b]
CL/F (L/h)	22.7	0.252	(22.6-22.8)	23.7	(23.2-24.2)
CL/F, BMI	−0.428	12.9	(−0.536 to −0.320)	−0.459	(−0.579 to −0.348)
CL/F, ALP	−0.118	21.3	(−0.167 to −0.069)	−0.279	(−0.34 to −0.22)
CL/F, elderly	0.739	0.307	(0.735 to −0.753)	0.713	(0.680-0.714)
V2/F (L)	9.09	0.0909	(9.07-9.11)	11.4	(8.62-14.25)
Q3/F (L/h)	32.1	0.0417	(32.1-31.1)	33.0	(30.68-35.94)
V3/F (L)	278	0.0156	(278-278)	289	(254-322)
Q4/F (L/h)	31.0	0.0997	(30.9-31.1)	30.1	(26.9-32.7)
V4/F (L)	783	0.0815	(782-784)	779	(732-832)
D1, capsule (h)	0.467	Fixed			
D1, tablet	0.254	Fixed			
D1, nighttime dosing	2.33	Fixed			
K_a, capsule (h^{-1})	0.532	Fixed			
K_a, tablet	1.12	Fixed			
K_a, food	0.695	Fixed			
ALAG1 (h)	0.403	Fixed			
F1, food	1.21	Fixed			
Interindividual variability (%CV)					
CL/F	48.1	3.68	(45.1-51.1)	46.8	(44.7-49.3)
V2/F	142	23.2	(86.7-197.3)	131	(107-158)
Q3/F	56.8	17.2	(40.4-73.2)	42.6	(32.1-50.4)
V3/F	82.0	15.0	(61.3-103)	66.1	(58.9-73.0)
Q4/F	46.5	11.4	(37.6-55.4)	52.0	(41.6-64.0)
V4/F	41.4	10.5	(34.1-48.7)	38.3	(33.5-44.1)
D1	167	Fixed			
K_a	43.8	Fixed			
F1	68.1	Fixed			
Residual variability					
Proportional (TAD > 3 h), % CV	14.3	1.07	(14.0-14.6)	14.3	(13.4-15.0)
Additive (TAD >3 h), ng/mL	0.0189	21.2	(0.012-0.026)	0.0203	(0.011-0.026)
Proportional (TAD ≤ 3 h), % CV	32.9	1.19	(32.2-33.6)	33.2	(32.1-34.4)
Additive (TAD ≤3 h), ng/mL	2.62	3.15	(2.48-2.76)	2.46	(0.44-3.51)

ALAG1, absorption lag time; CI, confidence interval; CL/F, apparent oral clearance; CV, square root of variance × 100; % RSE, percent relative standard error of the estimate = SE/parameter estimate × 100; D1, duration of absorption; F1, relative bioavailability; Ka, first-order absorption rate constant; Q2/F, central intercompartment clearance; Q3/F, peripheral intercompartment clearance; 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.

Continuous covariate fixed effects were parameterized assuming an exponential relationship.

$\theta_k = \theta_{TV,k} \cdot \left(\frac{cov_{i,cont}}{ref_{cont}}\right)^{\theta_{k,cont}}$, where $\theta_{TV,k}$ represents the typical (population) average parameter estimate for model parameter θ_k, $cov_{i,cont}$ is the *cont*th continuous covariate value in the *i*th subject, ref_{cont} is the generally centered reference value for the cont-continuous covariate, and $\theta_{k,cont}$ is the estimate of the continuous covariate for the *k*th PK parameter, θ_k. Dichotomous categorical covariates were parameterized as $\theta_j = \theta_{TV,j} \cdot \theta_{j,cat}^{cov_{i,cat}}$, where $\theta_{TV,j}$ represents the typical (population) average parameter estimate for model parameter θ_j, $\theta_{j,cat}$ is the *cat*th categorical covariate estimate and $cov_{i,cat}$ is the categorical covariate value for the *i*th subject.

[a] CIs based on standard errors from NONMEM (variance-covariance matrix) of estimates.

[b] CIs based on percentile confidence intervals from 250 final model bootstrap runs using PsN (Perl Speaks NONMEM).

the model based on the statistical significance criteria. Differences between Japanese and predominantly white (non-Japanese) subjectsand the effect of dose and sex in the model were minimal (Supplemental Figure S4).

A range of lemborexant exposures were simulated assuming 5-mg bedtime steady-state dosing (Table 3). Comparisons of 90%CIs for the difference in exposure log(AUC$_{ss}$) focused on (1) underweight (median BMI, 17.4 kg/m^2), overweight (median BMI, 27.4 kg/m^2), and obese (median BMI, 32.7 kg/m^2) versus normal subjects (median BMI, 22.9 kg/m^2) and (2) overweight elderly (>65 years) versus adults (≤65 years, as a reference). As expected, simulated lemborexant exposure following

5-mg nightly dosing in overweight individuals were noted to be additively higher (ratio, 139%; 90%CI, 129%-150%) in the elderly compared with adults with normal BMI (ratio, 119%; 90%CI, 111%-128%), providing an impetus to evaluate these covariate effects in the context of the exposure-response of key adverse events.

Relationship of Lemborexant Exposure and Treatment-Emergent Adverse Events

Adverse events from a 15-day treatment of 291 adults and elderly subjects with chronic insomnia with placebo and 1, 2.5, 5, 10, or 25 mg lemborexant (study 201,
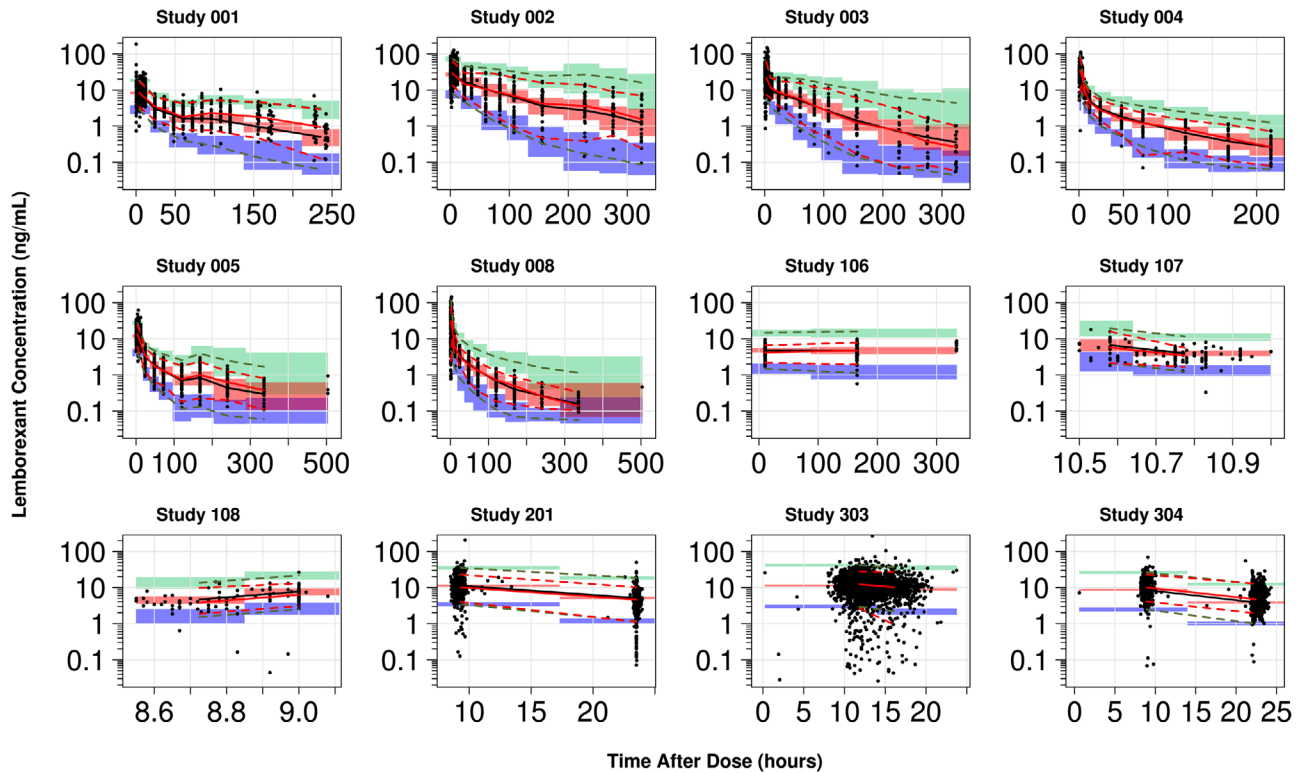
Figure 2. Lemborexant population pharmacokinetic prediction corrected visual predictive check plots stratified by study. Prediction corrected predictive check plots created using PSN VPC with 200 samples of the original data set stratified by study and PRED-level correction. Red lines depict quantiles of observed data at the 5th and 95th (dashed) and 50th (solid) percentiles binned over time after dose intervals of the study. Simulated data are binned across the same intervals and corresponding 90% prediction interval for each bin is depicted by distinct rectangles: blue, red, and green at the 5th, 50th, and 95th levels with median prediction interval for each level depicted in black: 5th and 95th (dashed) and the 50th (solid).

NCT01995838) indicated that the most common TEAE ($\geq$5% incidence in any lemborexant treatment group) was somnolence.[33] This TEAE appeared dose related, with a frequency ranging from 3.1% in the 1-mg group to 22.0% in the 25-mg group. Other TEAEs such as headache, sleep paralysis, abnormal dreams, dizziness, back pain, hallucinations, myalgia, and feeling drunk did not exhibit a clear dose-response pattern, usually exceeding the 5% incidence threshold in only a single treatment group.

Average steady-state lemborexant exposures derived from the population PK model were used to assess their association with TEAEs in adults and the elderly with chronic insomnia based on data from phase 3 studies SUNRISE 2 (study 303, n = 726) and SUN-RISE 1 (study 304, n = 524) and a phase 2 study for the treatment of irregular sleep-wake rhythm disorder (study 202, n = 62), which included elderly subjects. Available treatments ranged from 5 to 15 mg lemborexant or placebo. Six TEAEs were reported to occur in more than 30 subjects, chosen as a threshold for this analysis: headache, nasopharyngitis, somnolence, flu/influenza, urinary tract infection, and upper respiratory tract infection. The frequency of subjects experiencing these TEAEs ranged from approximately

3% to 8%: headache (n = 132; 7.8% placebo, 8.2% active treatment), nasopharyngitis (n = 132; 7.7% placebo, 8.6% active treatment), somnolence (n = 126; 8.5% placebo, 5.3% active treatment), flu/influenza (n = 54; 2.9% placebo, 4.0% active treatment), urinary tract infection (n = 44; 2.7% placebo, 2.5% active treatment), and upper respiratory tract infection (n = 56; 3.5% placebo, 3.2% active treatment).

There was a generally very shallow relationship of TEAEs and lemborexant exposure ($C_{av,ss}$), reflected in small OFV decreases for models containing an exposure predictor versus a reduced model (excluding $C_{av,ss}$), and neither was statistically or clinically significant. The models included age, sex, and race as covariates and considered interaction terms for sex, exposure, and age. $C_{av,ss}$ was not a statistically significant predictor of incidence of experiencing somnolence, nasopharyngitis, flu/influenza, urinary tract infection, or upper respiratory tract infection, with incidence in the range of those estimated for placebo treatment. Table 4 depicts the predicted exposure-TEAE response relationships for a 75-year-old white woman. Small, not statistically significant differences for the incidence of somnolence were noted for Japanese or African American subjects versus the reference group (whites)
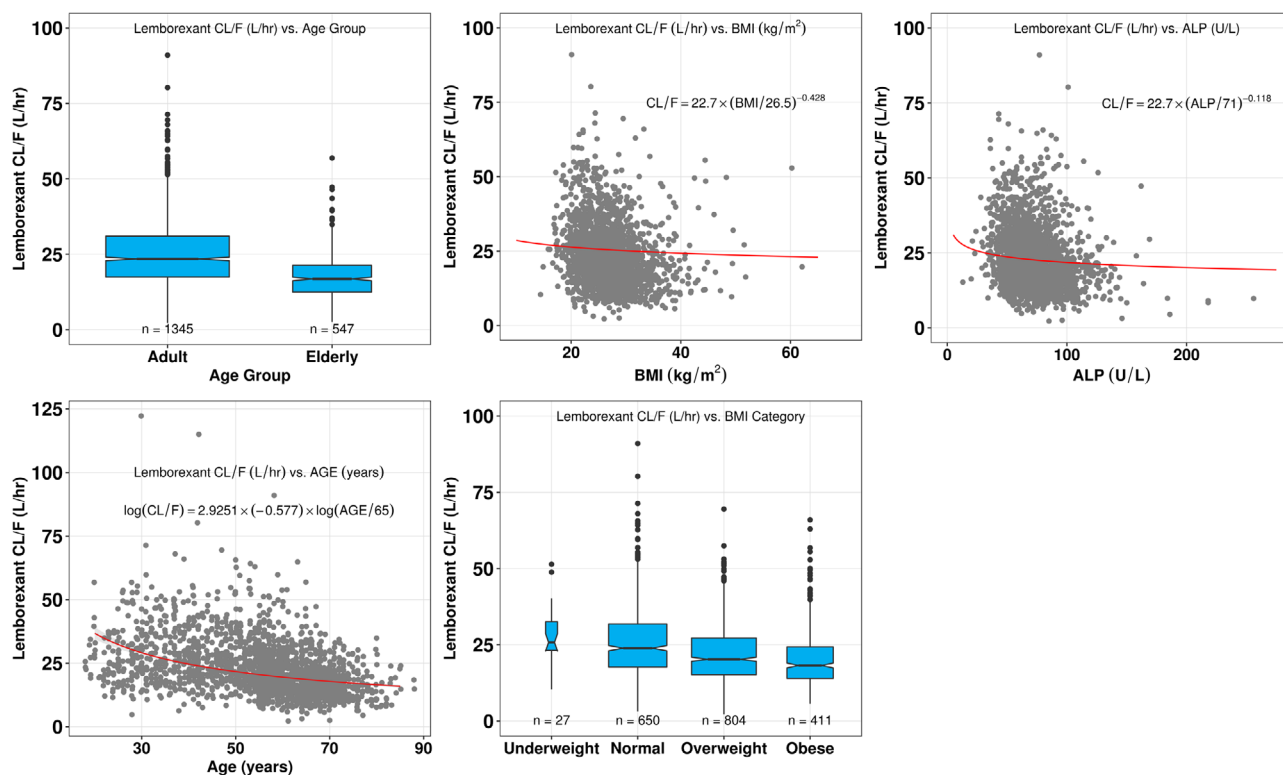
Figure 3. The relationship of the covariates of the lemborexant population pharmacokinetic model and individual-level lemborexant apparent oral clearance (CL/F) predictions. BMI, body mass index.

across the age range of the analysis and in men versus women.

For headache, lemborexant $C_{av,ss}$ was a weakly significant predictor (at the $P < .05$ level); however, the probability of experiencing this adverse event was noted to decrease with increasing exposure under the linear logit model (Table 4). Across the TEAEs (placebo and treatment), women reported a statistically significant lower incidence of headaches and a higher incidence of urinary tract infections. Except for urinary tract infections, incidence of all TEAEs decreased with age. A lower incidence ($<0.25\%$) of all TEAEs was observed for African American versus white subjects. Except for nasopharyngitis, TEAEs reported by Japanese subjects were also generally lower than by white subjects, without a significant difference.

Discussion

Lemborexant population pharmacokinetics were best described by a 3-compartment disposition model with combined first- and zero-order absorption with lag time and linear elimination from the central compartment. The model adequately described both extensively and sparsely sampled healthy-subject profiles and data from subjects with insomnia. Lemborexant was found to typically exhibit a CL/F of 23 L/h and a high steady-state volume of distribution of approximately 1000 L, characterized by a multiphasic profile (Table 2, Figure 2, Supplemental Figure S4). Lemborexant CL/F was dose independent and not significantly affected by race, sex, body weight, creatinine clearance, or liver enzymes (with the exception of a small effect of ALP) or concomitant PPIs. Exposures were predicted to be highest in the elderly (≥ 65 years) and obese subjects typically by 39% over adults of normal BMI. Subjects with ALP levels at the upper range of normal were predicted to result in a 7% higher CL/F over the typical subject. These higher exposures in the elderly and subjects with higher BMI and ALP potentially stem from decreased hepatic blood flow, decreasing hepatic mass, and/or decreasing first-pass metabolism.[34] Limitations were recognized in the assessment of several covariate effects of interest. The effect of PPIs was not evaluated on absorption parameters (D1 and K_a) because of the absence of information regarding the exact dosing of concomitant PPIs and the absence of sampling during the absorption phase across late-stage trials. The effects of histamine H_2-receptor antagonist blockade were assessed in a phase 1 drug-drug interaction study with famotidine, which indicated a 27% decrease in lemborexant C_{max} and a 0.5-hour delay in the median t_{max}; no significant effect was observed on lemborexant AUC_{0-t} and AUC_{0-inf} (NCT03451110).[35]

Table 3. Comparison of Simulated Lemborexant Exposure (AUC$_{ss}$) Across Categories of BMI and Elderly Overweight Versus Normal BMI Adult Subjects

| Dose (mg) | ln(AUC$_{ss}$) | | Ratio, % | Lower 90%CI | Upper 90%CI |
	Test	Reference			
5		Underweight (BMI 17.4 kg/m^2)	89	83	96
	Normal (BMI 22.9 kg/m^2)	Overweight (BMI 27.4 kg/m^2)	111	103	119
		Obese (BMI 32.7 kg/m^2)	119	111	128
5	Elderly (>65 years old) Overweight (BMI 26.6 kg/m^2)	Adult (18-65 years old) Normal (BMI 22.9 kg/m^2)	139	129	150

AUC$_{ss}$, area under the curve in steady state; BMI, body mass index; CI, confidence interval.

Comparisons based on 250 representative subject resamples. Lemborexant exposures (AUC$_{ss}$) assumed a 5-mg nightly dose at steady state and population median alkaline phosphatase of 71 IU/L. The comparison was based on a 90%CI for the difference in ln(AUC$_{ss}$) of the test and reference.

Table 4. Estimates of TEAE Probability Across Exposures of 5 and 10 mg Lemborexant Based on a Logistic Regression Analysis of Data From Studies 202, 303, and 304, With the Model Assuming a Linear Logit Exposure-Response Relationship for a 75-Year-Old Woman

C$_{av,ss}$ (ng/mL)	LEM Dose (mg) or Placebo	Quantile of LEM C$_{ave,ss}$	Somnolence	Nasopharyngitis	Urinary Tract Infection	Influenza	Upper Respiratory Tract Infection	Headache
0.00	Placebo	—	5.3 (3.6-7.7)	8.6 (6.4-11.0)	2.5 (1.4-4.4)	4.0 (2.6-6.2)	3.2 (1.9-5.2)	8.2 (6.0-11.0)
6.30	5 mg Lemborexant	5th	7.2 (5.3-9.7)	10.0 (7.5-14.0)	2.0 (1.2-3.5)	3.8 (2.3-6.2)	4.7 (2.9-7.3)	11.0 (7.8-14.0)
7.90		25th	7.4 (5.7-9.7)	9.5 (7.3-12.0)	2.1 (1.3-3.5)	3.6 (2.3-5.5)	4.4 (2.9-6.4)	9.8 (7.6-13.0)
10.00		50th	7.7 (6.1-9.7)	8.9 (7.1-11.0)	2.3 (1.4-3.5)	3.4 (2.3-4.9)	4.1 (2.9-5.7)	9.2 (7.3-11.0)
14.00		75th	8.1 (6.6-9.9)	8.1 (6.6-9.8)	2.5 (1.7-3.6)	3.1 (2.2-4.3)	3.6 (2.7-4.9)	8.3 (6.8-10.0)
19.00		95th	8.9 (7.3-11.0)	6.7 (5.2-8.6)	2.9 (2.0-4.1)	2.6 (1.8-3.9)	3.0 (2.0-4.3)	6.8 (5.3-8.6)
12.00	10 mg Lemborexant	5th	7.7 (6.0-9.7)	8.9 (7.1-11.0)	2.2 (1.4-3.5)	3.4 (2.3-4.9)	4.1 (2.9-5.7)	9.2 (7.4-12.0)
17.00		25th	8.4 (6.9-10.0)	7.6 (6.2-9.3)	2.6 (1.8-3.7)	2.9 (2.1-4.1)	3.4 (2.5-4.6)	7.7 (6.3-9.4)
21.00		50th	8.9 (7.3-11.0)	6.7 (5.2-8.6)	2.9 (2.0-4.0)	2.6 (1.8-3.9)	3.0 (2.0-4.3)	6.8 (5.3-8.6)
27.00		75th	9.6 (7.6-12.0)	5.8 (4.0-8.1)	3.3 (2.2-4.9)	2.3 (1.3-4.0)	2.5 (1.5-4.3)	5.7 (4.0-8.1)
37.00		95th	11.0 (7.5-17.0)	4.0 (2.1-7.7)	4.4 (2.2-8.7)	1.7 (0.6-4.7)	1.7 (0.6-4.6)	3.9 (2.0-7.4)

C$_{av,ss}$, average steady-state concentration; LEM, lemborexant; TEAE, treatment-emergent adverse event.

Oral [^{14}C]lemborexant administered to healthy subjects (study E2006-A001-007, NCT02046213) indicated that at least 87% of the lemborexant dose is bioavailable, as unchanged lemborexant was not detected in urine, but was found as the major component in feces (13.0%). Metabolite profiling from the single ascending-dose study (study 001, NCT01463098) confirmed that <1% of the administered dose was recovered as unchanged drug in urine; the main elimination pathway of lemborexant was oxidative metabolism. The major metabolic pathways of lemborexant involve CYP3A-mediated oxidation of lemborexant dimethylpyrimidine moieties with subsequent glucuronidation. The effect of concomitantly administered moderate CYP3A inhibitors on lemborexant CL/F was not included as a covariate because of the small number of subjects in the PK data set (22 of 1892 subjects). CYP3A-mediated inhibition and induction of lemborexant metabolism were addressed as part of several stand-alone drug-drug interaction studies (NCT03440424

[E2006-A001-004], NCT03451110 [E2006-A001-012]). CYP3A inhibition and induction were also assessed using physiologically based PK modeling approaches.[36] These drug-interaction studies and resulting model-based analyses indicated a clinically meaningful interaction of lemborexant with moderate and strong CYP3A inhibitors and warranted a contraindication of lemborexant coadministration with moderate and strong CYP3A inhibitors.

This lemborexant population model did not incorporate the PK of lemborexant metabolites, as they were considered to provide a minor pharmacological effect at the site of action (central nervous system). In humans, 3 primary oxidative metabolites were identified with highest relative exposures attributed to the M10 metabolite, identified to be present in >10% of total drug-related exposure. Although this metabolite has comparable in vitro OXR1 and OXR2 affinity to the parent drug (IC_{50}, 4.2 and 2.9 nmol/L, respectively), it is not considered to significantly penetrate the blood-brain barrier based on its logP estimates. The calculated logP of M10 was estimated to be 1.57 versus 3.2 for the parent drug.[37] This model facilitated a closer examination of lemborexant PK parameters to offer a comparison with the PK of other insomnia treatments. Bedtime dosing of lemborexant is estimated to result in an accumulation ratio of 1.9 following once-daily dosing.[38,39] Lemborexant PK exhibits, on average, a 3.5- to 4-fold higher steady-state concentration at C_{max} compared with morning concentrations 8-9 hours post-dose. Similarly, 53%-57% of the area under the curve at steady state (AUC_{ss}) was eliminated by this postdose time. A review of microrate constants indicated that the fraction of the lemborexant alpha disposition phase was estimated to be at 99.4% of the total disposition AUC, beta and gamma half-lives contributing with 0.2% and 0.4% of the total dispositional AUC, respectively.

Multiphasic PK profiles are also reported for other dual orexin receptor antagonists including suvorexant, based on the population PK model as well as available data for daridorexant and seltorexant, based on multiple rising-dose phase 1 studies.[40-42] For benzodiazepines and Z-drugs, which are direct and partial receptor agonists of the GABAergic neurotransmitter pathways, the half-life is relatively short and compounds in these classes with longer half-lives (generally on the order of >6 hours) have exhibited adverse event liability with respect to potential daytime residual adverse effects such as nausea and somnolence and diminished postural stability at waketime.[15,42] As reported here, the half-life of lemborexant is much longer than conventional treatments, resulting in drug accumulation on multiple dosing and daytime drug exposure. However, reflecting the novel mechanism, the exposure-response analysis reveals no evidence of clinically important drug- or exposure-related activity relative to placebo. Although the time course of endogenous orexin/hypocretin has not been characterized in humans, diurnal variations of this endogenous ligand is well documented across animal species.[22,43] Thus, daytime dual orexin receptor antagonist concentrations are hypothesized to be countered by rising endogenous orexin in the morning and during the day, minimizing any residual daytime effects. For lemborexant, results from studies across its program support the negligible contribution of exposure in the morning to its pharmacodynamic effects.[44,45] A follow-up article will present the model-based exposure-response analyses of the association of lemborexant exposure and time with efficacy measures of sleep (polysomnography and sleep diary data) and postural stability safety measures (body sway).

With respect to lemborexant safety, TEAE incidence was previously summarized for 2 lemborexant studies.[21,33] These results were expanded on by an exposure-response analysis described here, which demonstrated a general lack of a clinically relevant association of lemborexant exposures with TEAEs across the therapeutic range cohort of elderly subjects receiving up to 5-15 mg. These TEAE models attempted to also delineate lemborexant exposure-response while taking into consideration the contribution of key clinical factors of elderly and sex. The models failed to detect notable differentiating trends or treatment effects that were notably higher than placebo, supporting a favorable safety profile of lemborexant. Headache, nasopharyngitis, flu/influenza, urinary tract infection, and upper respiratory tract infection are generally common adverse events, likely to be reported in longer-term trials in this population. As a caveat to this analysis, the TEAE logistic regression cannot adequately account for study duration. Smaller differences between the treatment and placebo somnolence rates were noted for the 9-month SUNRISE 2 study (11% vs 8.2%) versus the 1-month SUNRISE 1 study (5.6% vs 1.9%) and study 202 (6% vs 0%).

Conclusion

This model-based analysis identified small exposure increases in the elderly (26%) relative to an adult insomnia population using a 3-compartment linear-elimination model with combined first- and zero-order absorption with lag time. Lemborexant exposure is also mildly elevated in subjects with high BMI or ALP (up to 20% for obese subjects, 8% for high ALP subjects). The clinical relevance of these small covariate effect sizes impacting lemborexant exposure should be considered in the context of an essentially flat therapeutic exposure ($C_{av,ss}$)-TEAE relationship for somnolence,

nasopharyngitis, flu/influenza, urinary tract infection, upper respiratory tract infection, or headache. The incidence of identified TEAEs was similar for lemborexant exposure and placebo treatment across the 5- to 15-mg dose range studied across longer-term late-stage trials. As these analyses characterized a wide and generally exposure-independent safety window, a dose adjustment for lemborexant based on age, sex, or BMI is not considered to be warranted and indeed was not mandated in the recent approvals of lemborexant in the United States and Japan.

Conflicts of Interest

Funding

Data Sharing

Data and model code will be made available on request, per Eisai, Inc. practices and procedures.

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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.