


Effect of severe renal impairment on pharmacokinetics, safety, and tolerability of lemborexant

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Funding information

This study was financially supported by Eisai Inc., Woodcliff Lake, New Jersey, USA. Eisai Inc. is the owner and manufacturer of lemborexant. The investigators retained full independence in the conduct of this research.

Abstract

The primary aim of this study was to examine the effect of severe renal impairment (SRI) on the pharmacokinetics of lemborexant, a dual orexin receptor antagonist indicated for the treatment of insomnia. A phase 1 multicenter, single-dose, open-label, parallel-group study was conducted in subjects with SRI not requiring dialysis (estimated glomerular filtration rate 15–29 ml/min/1.73 m²; $n = 8$) compared with demographically matched healthy subjects with normal renal function ($n = 8$). Plasma levels of lemborexant and its metabolites were measured over 240 h following a single oral 10-mg dose administered in the morning. Relative to subjects with normal renal function, lemborexant maximum plasma concentration (C_{\max}) was similar, whereas area under the plasma concentration–time curve from zero to time of last quantifiable concentration ($AUC_{(0-t)}$) and AUC from zero to infinity ($AUC_{(0-inf)}$) were about 1.5-fold higher in subjects with SRI. The geometric mean ratios (90% confidence interval) were 104.8 (77.4–142.0), 150.5 (113.2–200.3), and 149.8 (113.1–198.6) for C_{\max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$, respectively. In both groups, the median lemborexant time to C_{\max} (t_{\max}) was 1 h, and the mean unbound fraction of lemborexant was ~7%. For the M4, M9, and M10 metabolites, C_{\max} was reduced ~20% and exposure ($AUC_{(0-t)}$ and $AUC_{(0-inf)}$) was ~1.4- to 1.5-fold higher in subjects with SRI versus healthy subjects; t_{\max} was delayed ~1.5–2 h for M4 and M10. All treatment-emergent adverse events were mild or moderate. Lemborexant pharmacokinetics were not sufficiently altered to warrant a dose adjustment for subjects with renal impairment.

KEYWORDS

chronic kidney disease, clinical pharmacology, drug safety, lemborexant, pharmacokinetics, phase 1, renal impairment

Abbreviations: $AUC_{(0-inf)}$, zero to infinity; $AUC_{(0-t)}$, zero to time of last quantifiable concentration; C_{\max} , maximum plasma concentration; eGFR, estimated based on glomerular filtration rate; SRI, severe renal impairment; TEAE, treatment-emergent adverse event.

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1 | INTRODUCTION

Insomnia is a prevalent sleep–wake disorder associated with negative impacts on overall physical and mental health¹ and increased health-care utilization and costs.^{2,3} **Lemborexant** (Dayvigo™) is a dual orexin receptor antagonist. Data from phase 1 and 2 studies have shown that on multiple dosing up to 25 mg/day, lemborexant is well tolerated, does not exert relevant effects on next-morning residual sleepiness, and provides a suitable pharmacokinetic profile for the target pharmacologic effect.^{4,5} In addition, results from phase 1 studies have shown that lemborexant, when administered at multiple doses up to 25 mg, has a linear PK profile.⁵ Lemborexant was recently approved in the United States,⁶ Japan, and Canada at doses up to 10 mg/day for the treatment of adult and elderly (≥65 years of age) persons with insomnia. Lemborexant is also in development for the treatment of irregular sleep–wake rhythm disorder. In the pivotal phase 3 trials of lemborexant for insomnia, Study E2006-G000-304 (SUNRISE-1; NCT02783729) and Study E2006-G000-303 (SUNRISE-2; NCT02952820), lemborexant treatment provided significant benefit on sleep onset and sleep maintenance compared with placebo at 1 month and 6 months, respectively.^{7,8} In both studies, lemborexant was well tolerated.^{7,8}

Mass balance studies in animal models have shown that lemborexant is primarily cleared by metabolism and has negligible urinary clearance.⁹ Similarly, in humans, renal elimination of lemborexant is low. In a phase 1 [¹⁴C]lemborexant mass balance study in healthy males (NCT02046213; E2006-A001-007), the majority of [¹⁴C]lemborexant-related materials were recovered in feces, accounting for approximately 57.4% of the total administered dose compared with 29.1% of the dose in urine.¹⁰ In addition, in metabolic profiling analyses from this study, lemborexant was not detected in urine, but was found as the major component (13.0% of the dose) in feces,¹⁰ which was likely derived from the unabsorbed fraction of [¹⁴C]lemborexant. Moreover, in a single-ascending dose study (NCT01463098; E2006-A001-001), less than 1% of the administered dose of lemborexant was recovered as unchanged drug in urine.¹¹ Taken together, these results indicate that urinary excretion of lemborexant is minor and that the main elimination pathway of lemborexant is metabolism. Similar to other dual orexin receptor antagonists,^{12,13} metabolism of lemborexant is predominately mediated by **CYP3A4**.^{6,14} Oxidation of lemborexant is primarily to the metabolites M4, M9, and M10. These metabolites, all of which are **P-glycoprotein** substrates, have binding affinities for **orexin receptors** that are similar to lemborexant. However, due to P-glycoprotein transport resulting in minimal brain penetration of the metabolites, their contribution to the pharmacological activity is thought to be minimal.¹⁰

Renal impairment can affect pharmacokinetic properties of drugs, even drugs that are not primarily eliminated renally.¹⁵ For example, renal impairment can influence the absorption, plasma protein binding, transport and/or tissue distribution of drugs that are mainly metabolized by the liver and intestine.^{16,17} Such alterations may be more pronounced in subjects with severe renal impairment (SRI), which may increase the risk of adverse reactions in those subjects.^{15,16} In addition, a large subset of the population affected by

What is already known about this subject

- Lemborexant is a dual orexin receptor antagonist approved in the United States and Japan for the treatment of adult and elderly persons with insomnia.
- Lemborexant is primarily metabolized by CYP3A4.
- Renal elimination is a minor clearance pathway for lemborexant.

What this study adds

- Lemborexant t_{max} and C_{max} were not altered in subjects with severe renal impairment, but exposure (AUC) was increased ~1.5-fold.
- For lemborexant metabolites, C_{max} values were reduced by about 20%–30% and AUCs were ~1.4–1.5 higher in subjects with severe renal impairment.
- Dosing adjustment is not required for subjects with renal impairment.

insomnia may have renal impairment or other impairments in the gut or hepatic systems that can influence renal pathway elimination.¹⁸ Thus, although renal clearance is a minor elimination pathway for lemborexant, given the broader impact of renal impairment on non-renal clearance mechanisms, an assessment of lemborexant pharmacokinetics was undertaken in subjects with SRI.

The primary objective of this phase 1 study (NCT03443063; E2006-A001-105) was to evaluate the effect of SRI on the pharmacokinetic properties of lemborexant after a single dose. The secondary objectives were as follows: to assess the effect of SRI on the pharmacokinetics of the unbound fraction of lemborexant; to assess the effect of SRI on the pharmacokinetics of the M4, M9, and M10 metabolites of lemborexant; and to assess the safety and tolerability of lemborexant in subjects with normal renal function or with SRI.

2 | METHODS

The study was approved by an institutional review board and followed principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice Guidelines, and the Declaration of Helsinki. Prior to any screening procedures, the investigator or qualified designee obtained written informed consent from each subject. The study was conducted between February 7, 2018 and August 24, 2018 at two sites in the United States.

2.1 | Subjects

Subjects were 18–79 years of age with a body mass index between 18 and 40 kg/m² and normal liver function. Males and females were

eligible for the study. Subjects' renal function was estimated based on glomerular filtration rate (eGFR) from serum creatinine using the Modification of Diet in Renal Disease formula.¹⁹ Subjects with SRI were enrolled first, had an eGFR 15–29 ml/min/1.73 m², and were not on dialysis. Healthy control subjects were matched demographically (race, sex, age \pm 10 years, and body mass index \pm 20%) and had normal renal function (eGFR \geq 90 ml/min/1.73 m²).

Exclusion criteria included women who were pregnant or breastfeeding, positive HIV status, acute liver disease or injury, prolonged QT/QTc interval, and drug or alcohol use disorder. Additional exclusion criteria for subjects with SRI included history of renal transplant and significant bleeding diathesis. The full list of inclusion and exclusion criteria is available on clinicaltrials.gov.

2.2 | Study design

This was a multicenter, single-dose, open-label, parallel-group phase 1 study. Subjects were administered a single oral dose of lemborexant 10 mg in the morning of day 1 following an overnight fast. Subjects were monitored in the clinic until day 8 and returned to the clinic for additional assessments on day 11. The lemborexant 10 mg dose was selected because, at the time of this study, it was the highest dose being studied in phase 3 trials. The 10 mg dose has since been approved as the highest dose for the treatment of subjects with insomnia.

All subjects were prohibited from having foods, beverages, or supplements that affect **CYP3A enzymes**, such as St. John's wort or grapefruit-containing foods, within 2–4 weeks before drug administration.

2.3 | Bioanalytical methods and pharmacokinetic assessments

Blood samples (4 ml each) were collected at predose and up to 240 h postdose for pharmacokinetic analyses of lemborexant and its metabolites. In addition, blood samples (12 ml each) were collected for plasma protein-binding assessments of lemborexant at 1 and 24 h postdose. All samples were collected with sodium heparin as an anticoagulant.

Total plasma concentrations of lemborexant and the M4, M9, and M10 metabolites were measured by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method following liquid-liquid extraction. Analyses were conducted with a SCIEX API-5500 Triple Quad mass spectrometer (SCIEX, Framingham, Massachusetts, USA) coupled with a Shimadzu LC system (Shimadzu Corporation, Kyoto, Japan) (Phenomenex [Torrance, California, USA] Kinetex 5 μ m XB-C18 100A 250 \times 4.6 mm chromatography column with a mobile-phase gradient) in positive electrospray ionization mode. The multiple reaction monitoring transition was mass-to-charge ratio (m/z) 411.0 \rightarrow 287.1 for lemborexant,⁵ 427.0 \rightarrow 287.1 for M4, M9, and M10, and 414.0 \rightarrow 290.1 for the deuterated internal standard lemborexant-d₃,⁵ M4-d₃, M9-d₃, and M10-d₃. For all analytes, the lower limit of quantitation was 0.0500 ng/ml with the calibration curve ranging from 0.0500 to 50.0 ng/ml. Dilution of samples originally above the upper limit of the

calibration range was validated by analyzing six replicate quality controls containing 500 ng/ml lemborexant as 10-fold dilutions. The validated method had an inter-day and intra-day precision and accuracy of less than 14.7% across all analytes, with incurred sample reanalysis passing acceptance criteria²⁰ in study samples. Long-term sample stability was established up to 34 months in frozen human plasma at -70°C . Plasma protein unbound fraction (f_u) of lemborexant was determined by a similar validated LC-MS/MS method following an equilibrium dialysis using a cellulose membrane with a 14 000 Dalton molecular weight cutoff (Viskase, Lombard, Illinois, USA).

Pharmacokinetic parameters were derived from plasma concentrations by noncompartmental analysis using Phoenix WinNonlin (Phoenix 64, version 6.3 by Pharsight, Certara, L. P., Princeton, New Jersey, USA). Plasma pharmacokinetic parameters included maximum plasma concentration (C_{\max}), time to C_{\max} (t_{\max}), area under the plasma concentration–time curve from zero to infinity ($\text{AUC}_{(0-\infty)}$), and area under the plasma concentration–time curve from zero to the time of the last quantifiable concentration ($\text{AUC}_{(0-t)}$). Apparent plasma clearance of drug after extravascular administration (CL/F) was calculated for lemborexant only by dividing the dose by $\text{AUC}_{(0-\infty)}$.

2.4 | Safety

Safety was assessed by monitoring treatment-emergent adverse events (TEAEs), electrocardiograms, vital signs, weight, physical examinations, and clinical laboratory tests (urinalysis, hematology, and blood chemistry).

2.5 | Statistical analysis

A sample size of eight subjects per cohort was based on recommendations in regulatory guidelines for the minimum number of subjects needed to be dosed in an SRI cohort.¹⁵ Based on data from previous single-dose studies of lemborexant 10 mg, the pooled between-subject standard deviation of logarithmically transformed $\text{AUC}_{(0-\infty)}$ values of lemborexant is 0.391. With a sample size of eight subjects with SRI and eight matched controls, the two-sided 90% confidence interval (CI) for the geometric mean ratio (GMR) for $\text{AUC}_{(0-\infty)}$ would extend from 0.72 to 1.38 (for a mean ratio of 1.0). Similar precision was expected for the two-sided 90% CI for the ratio for $\text{AUC}_{(0-t)}$.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Demographics and baseline characteristics were summarized for each renal function group using descriptive statistics. Pharmacokinetic parameters were summarized separately for subjects with SRI and subjects with normal renal function.

The effect of renal impairment on the pharmacokinetics of lemborexant was assessed using a linear model with renal impairment as a factor. Logarithmically transformed values of C_{\max} , $\text{AUC}_{(0-t)}$, and $\text{AUC}_{(0-\infty)}$ were utilized to estimate the GMR and two-sided 90% CI of subjects with SRI versus subjects with normal renal function.

Similar statistical analyses were conducted for the pharmacokinetic parameters of lemborexant metabolites.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,²¹ and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.²²

3 | RESULTS

3.1 | Subject disposition and baseline characteristics

Eight subjects were enrolled per group, all received one dose of lemborexant 10 mg and all completed the study. All subjects were male and White, and mean age and other characteristics were similar between groups (Table 1).

Parameter	Normal renal function (n = 8)	Severe renal impairment (n = 8)	Overall (N = 16)
Age, mean (SD), y	66.5 (7.9)	67.4 (5.4)	66.9 (6.6)
Male sex, n (%)	8 (100)	8 (100)	16 (100)
White race, n (%)	8 (100)	8 (100)	16 (100)
Hispanic or Latino ethnicity, n (%)	5 (62.5)	5 (62.5)	10 (62.5)
Weight, mean (SD), kg	83.33 (9.88)	85.00 (12.72)	84.16 (11.04)
Height, mean (SD), cm	172.41 (10.24)	169.89 (8.05)	171.15 (9.00)
BMI, mean (SD), kg/m ²	28.04 (2.39)	29.54 (4.88)	28.79 (3.79)
eGFR, mean (SD), ml/min/1.73 m ²	114.63 (16.14)	23.25 (3.92)	68.94 (48.53)

BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.

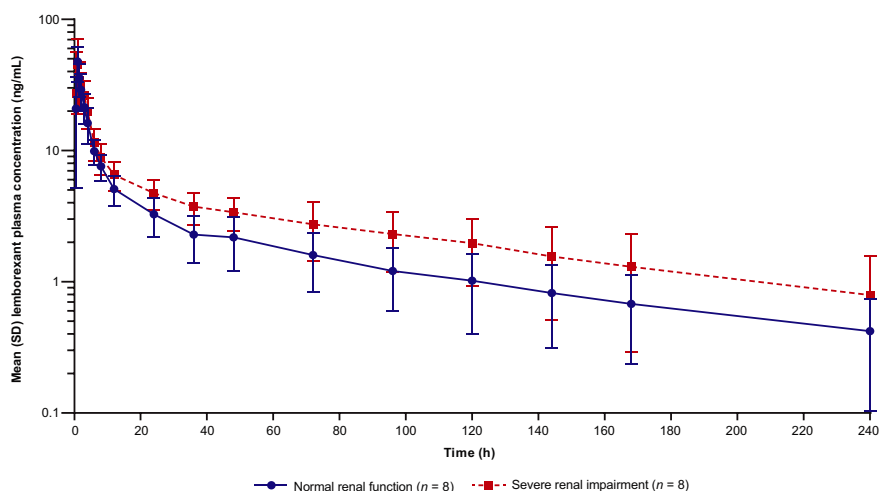


TABLE 1 Demographics and baseline characteristics

3.2 | Pharmacokinetic assessments

Mean lemborexant plasma concentrations were similar between groups through 24 h postdose; thereafter, mean concentrations were higher among subjects with SRI compared with healthy subjects with normal renal function (Figure 1).

Mean lemborexant C_{max} was similar (approximately 1.05-fold higher) for subjects with SRI and subjects with normal renal function (Table 2; Figure 2A), and occurred at a median t_{max} of 1 h in both groups (Table 2). C_{max} values for individual subjects were within the same general range in both groups (Figure 2B). Mean lemborexant $AUC_{(0-inf)}$ and $AUC_{(0-t)}$ values were approximately 1.5-fold higher in subjects with SRI compared with subjects with normal renal function (Table 2; Figure 2A). Correspondingly, the individual $AUC_{(0-inf)}$ values spanned a higher range in the SRI subjects versus the healthy subjects (Figure 2C). CL/F of lemborexant was reduced by approximately 33% in subjects with SRI versus subjects with normal renal function (Table 2). In both groups, the mean fu was approximately 7% (Table 2).

Mean C_{max} was approximately 20% lower for the M4 and M9 metabolites and 27.5% lower for M10 (Table 2; Figure 3). For all three metabolites, mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values were approximately

FIGURE 1 Mean (±SD) plasma lemborexant concentration-time profiles after administration of lemborexant 10 mg to healthy subjects with normal renal function or subjects with severe renal impairment. SD, standard deviation

TABLE 2 Geometric mean (% CV) of pharmacokinetic parameters of lemborexant and lemborexant metabolites M4, M9, and M10 after administration of lemborexant 10 mg to subjects with normal renal function or severe renal impairment

Parameter	Normal renal function (n = 8)	Severe renal impairment (n = 8)
Lemborexant		
t_{max} , h ^a	1.00 (1.00–1.50)	1.00 (0.50–3.00)
C_{max} , ng/ml	46.6 (29.2)	48.9 (41.0)
$AUC_{(0-inf)}$, h·ng/ml	449 (38.3) ^b	672 (19.6) ^b
CL/F, L/h	22.3 (38.3) ^b	14.9 (19.6) ^b
fu, %	7.11 (10.7)	6.68 (10.4)
M4		
t_{max} , h ^a	2.00 (1.00–4.00)	3.50 (1.00–4.00)
C_{max} , ng/ml	7.96 (39.5)	6.37 (44.8)
$AUC_{(0-inf)}$, h·ng/ml	179 (29.9) ^b	248 (20.4) ^b
MPR $AUC_{(0-inf)}$	0.384 (13.6) ^b	0.355 (7.49) ^b
M9		
t_{max} , h ^a	1.25 (1.00–2.00)	1.00 (1.00–4.00)
C_{max} , ng/ml	4.74 (45.9)	3.77 (44.1)
$AUC_{(0-inf)}$, h·ng/ml	73.5 (38.8) ^b	108 (24.1) ^b
MPR $AUC_{(0-inf)}$	0.150 (31.7) ^c	0.155 (18.5) ^b
M10		
t_{max} , h ^a	3.00 (2.00–4.00)	5.00 (3.00–72.17)
C_{max} , ng/ml	3.83 (48.0)	2.78 (50.5)
$AUC_{(0-inf)}$, h·ng/ml	262 (36.7) ^c	357 (20.1) ^d
MPR $AUC_{(0-inf)}$	0.612 (10.3) ^c	0.549 (13.4) ^d

$AUC_{(0-inf)}$, area under the concentration–time curve from zero to infinity; CL/F, apparent plasma clearance of drug after extravascular administration; C_{max} , maximum plasma concentration; CV, coefficient of variation; fu, fraction of total drug that is unbound in plasma; MPR $AUC_{(0-inf)}$, ratio of $AUC_{(0-inf)}$ of individual metabolite to $AUC_{(0-inf)}$ of lemborexant, corrected for molecular weights; t_{max} , time to maximum plasma concentration.

^aPresented as median (range).

^bn = 7, terminal rate could not be estimated for one subject.

^cn = 6, terminal rate could not be estimated for two subjects.

^dn = 5, terminal rate could not be estimated for three subjects.

1.4- to 1.5-fold higher based on the GMRs for subjects with SRI versus healthy subjects (Table 2; Figure 3). Median t_{max} for M4 and M10 was delayed 1.5 and 2 h, respectively, in subjects with SRI compared with the corresponding values in healthy subjects with normal renal function; median t_{max} values for M9 were similar in both groups (Table 2). The metabolite-to-parent ratio of $AUC_{(0-inf)}$ was similar between groups for each metabolite (Table 2).

3.3 | Safety

The incidence of TEAEs was similar between groups: five subjects (62.5%) with SRI and seven subjects (87.5%) with normal renal function experienced at least one TEAE. All TEAEs were mild or

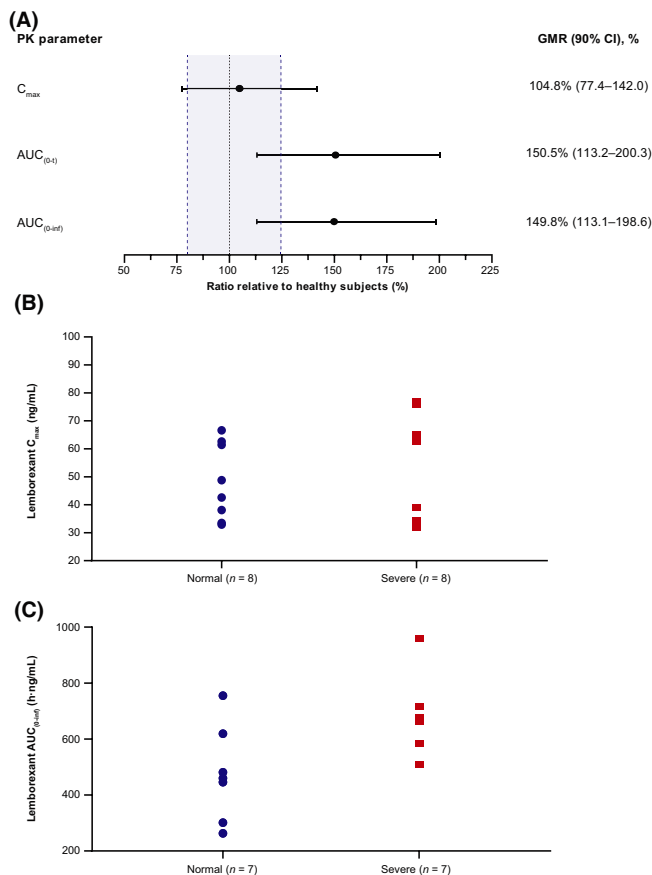


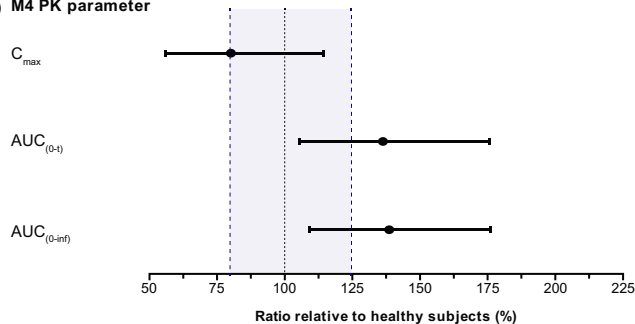
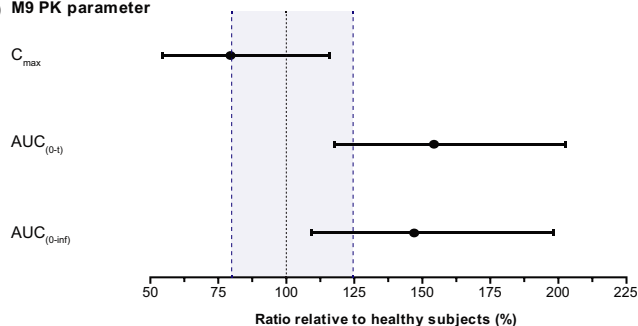
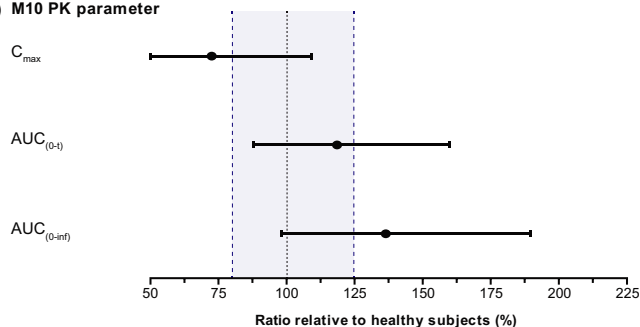
FIGURE 2 PK parameters of lemborexant 10 mg for subjects with severe renal impairment versus healthy subjects with normal renal function. (A) Forest plot of GMR (90% CI) for C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. (B) C_{max} values for individual subjects. (C) $AUC_{(0-inf)}$ values for individual subjects. $AUC_{(0-inf)}$, area under the concentration–time curve from zero to infinity; AUC_{0-t} , area under the concentration–time curve from zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max} , maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

moderate in severity. No serious TEAEs occurred, and no TEAE led to study discontinuation.

All subjects who experienced a TEAE (n = 12) experienced somnolence; one subject in the SRI group also experienced chills. Occurrence of somnolence was expected because lemborexant is a sleep-promoting drug that was administered in the morning.

4 | DISCUSSION

Lemborexant is predominantly metabolized by nonrenal CYP3A-mediated elimination pathways. Although renal clearance is not the primary clearance mechanism for lemborexant,⁹ examining the potential impact of impaired kidney function on lemborexant pharmacokinetics and safety was important given that chronic renal failure can alter the pharmacokinetics of drugs predominantly metabolized by the liver.¹⁶

(A) M4 PK parameter**(B) M9 PK parameter****(C) M10 PK parameter****GMR (90% CI), %**

80.1% (56.1–114.4)

136.3% (105.6–175.9)

138.6% (109.1–176.1)

GMR (90% CI), %

79.5% (54.5–116.0)

154.3% (117.5–202.6)

147.0% (109.1–198.2)

GMR (90% CI), %

72.5% (48.1–109.3)

118.5% (87.8–160.0)

136.4% (98.2–189.5)

FIGURE 3 PK parameters of lemborexant metabolites for subjects with severe renal impairment versus healthy subjects with normal renal function. Forest plots of GMR (90% CI) for C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ for (A) M4, (B) M9, and (C) M10. $AUC_{(0-inf)}$, area under the concentration–time curve from zero to infinity; $AUC_{(0-t)}$, area under the concentration–time curve from zero to the time of the last quantifiable concentration; CI, confidence interval; C_{max} , maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

In this phase 1 study, SRI did not alter the rate of absorption of lemborexant (t_{max}) and had no effect on C_{max} . However, approximately 1.5-fold higher exposure ($AUC_{(0-t)}$ and $AUC_{(0-inf)}$) of lemborexant was observed in subjects with SRI compared with subjects with normal renal function. Plasma protein binding of lemborexant did not differ between healthy subjects and subjects with SRI; the mean f_u was approximately 7% for both groups. For the M4, M9, and M10 metabolites, SRI was associated with approximately 20%–30% lower C_{max} values and approximately 1.4- to 1.5-fold higher $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values. For each metabolite, the metabolite-to-parent ratio was similar between groups, demonstrating no apparent effect of SRI on the extent of lemborexant metabolism. Based on the multiexponential profile of lemborexant, effective half-life, which is determined using drug concentration–time data following steady-state dosing, is a clinically relevant measure of half-life since it takes into account accumulation of the drug. The effective half-life for lemborexant was calculated in a study enrolling healthy volunteers to be between 17 and 19 h.⁵ Because this study was conducted following a single dose of lemborexant, effective half-life is not reported here.

Overall, the results from this study suggest that SRI largely affects elimination, but not absorption of lemborexant, and are consistent with renal excretion being a minor clearance pathway. The increase in exposure to lemborexant and its metabolites in subjects with SRI may result, at least in part, from the effect of renal impairment on nonrenal processes such as metabolism and transport.

Although an approximate 1.5-fold increase in exposure ($AUC_{(0-inf)}$) was observed in subjects with SRI, a dose adjustment in subjects with mild, moderate, or severe renal impairment is not considered warranted.⁶ This recommendation is supported by safety data for lemborexant in healthy subjects and subjects with insomnia.^{4,5,7,8,23} Importantly, safety results from phase 1 studies have shown that at doses up to 25 mg, lemborexant exhibits its minimal pharmacologic liability during waketime, supporting a sufficiently wide margin of safety relative to the highest approved dose of 10 mg.⁵ In this study, single doses of lemborexant 10 mg were well tolerated by subjects with normal or severely impaired renal function. The frequency of TEAEs was similar between groups, and all TEAEs were mild or moderate in severity.

However, because of the increase in exposure, subjects with SRI may be at a higher risk of experiencing TEAEs such as somnolence than persons with normal renal function.⁶

This study was conducted in accordance with the 2010 FDA guidelines for examining the PK of drugs in subjects with renal impairment.¹⁵ The FDA guidelines indicate that the control (normal renal function) group should ideally be representative of the target patient population. The enrollment criteria for this study did not limit participation based on sex or race. Subjects with SRI were enrolled first and control subjects were then enrolled who closely matched the SRI subjects with respect to age, race, sex, and BMI. In this study, all SRI subjects were White and male, thus, the control group also comprised White male subjects. Prior population PK modeling analyses demonstrated no clinically important effect of sex on lemborexant PK.²⁴ Therefore, the results from this study are also applicable to females with renal impairment.

In conclusion, the results of this study support the use of lemborexant in subjects with mild to severe renal impairment without the need for a dose adjustment.

5 | PRINCIPAL INVESTIGATOR STATEMENT

The authors confirm that the Principal Investigators for this paper were Kenneth Lasseter and Thomas Marbury and that they had direct clinical responsibility for patients. This phase 1 study was conducted at two clinical research organization sites in the United States, Orlando Clinical Research Center and Clinical Pharmacology of Miami. The Eisai Inc. responsible medical officer Gleb Filippov is included as an author.

ACKNOWLEDGEMENTS

The authors thank Jim Ferry of Eisai Inc. for his contributions to this manuscript. Medical writing assistance was provided by Jeanne McKeon, PhD, of ProScribe – Envision Pharma Group, and was funded by Eisai Inc. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

CONFLICT OF INTEREST

Ishani Landry, Jagadeesh Aluri, Nancy Hall, Gleb Filippov, Margaret Moline, and Larisa Reyderman are employees of Eisai Inc. Satish Dayal is an employee of Eisai Ltd.

AUTHORS' CONTRIBUTIONS

All authors have: made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICS STATEMENT

The study was approved by an institutional review board and followed the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice Guidelines, and the Declaration of Helsinki. Prior to any screening procedures, the investigator or qualified designee obtained written informed consent from each subject.

DATA AVAILABILITY STATEMENT

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

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How to cite this article: Landry I, Aluri J, Hall N, et al. Effect of severe renal impairment on pharmacokinetics, safety, and tolerability of lemborexant. *Pharmacol Res Perspect.* 2021;9:e00734. <https://doi.org/10.1002/prp2.734>