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ORIGINAL ARTICLE

Effect of hepatic impairment on pharmacokinetics, safety, and tolerability of lemborexant

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Abstract

Lemborexant, a dual orexin receptor antagonist, is approved in the United States, Japan, and Canada for the treatment of insomnia in adults. This phase I, multicenter, open-label, parallel-group study assessed the impact of mild or moderate hepatic impairment (HI) on lemborexant pharmacokinetics and metabolism. The pharmacokinetics, tolerability, and safety of lemborexant were evaluated in subjects with mild (Child–Pugh class A) or moderate (Child–Pugh class B) HI and healthy age-, sex-, and body mass index (BMI)-matched control subjects (n = 8 subjects/group). Subjects received a single oral dose of lemborexant 10 mg (LEM10). Blood samples were collected up to 312 hours post dosing for lemborexant pharmacokinetics assessments. Median time to maximum plasma concentration was similar across all groups. Compared with healthy subjects, exposure measures (maximum plasma concentration [C_{max}] and area under the curve extrapolated to infinity [$AUC_{0\text{-}inf}$]) increased by ~58% (C_{max}) and ~25% ($AUC_{0\text{-}inf}$) in subjects with mild HI and ~22% (C_{max}) and ~54% ($AUC_{0\text{-}inf}$) in subjects with moderate HI. Clearance decreased by 20% and 35% in subjects with mild and moderate HI, respectively, versus healthy subjects. Lemborexant unbound fraction was similar in all groups (range: 0.060–0.065). All treatment-emergent adverse events (TEAEs) were mild in severity; no serious TEAEs occurred. In conclusion, following a single LEM10 dose, lemborexant exposure was similar in subjects with mild HI and increased in subjects with moderate HI versus healthy subjects. No dose adjustment is required in subjects with mild HI. Dosing in subjects with moderate HI should be restricted to 5 mg. Lemborexant was well tolerated in all groups.

KEYWORDS
drug safety, dual orexin receptor antagonist, hepatic impairment, lemborexant, pharmacokinetics

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; $AUC_{0\text{-}inf}$, area under the curve extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; BMI, body mass index; CI, confidence interval; CL/F, apparent body clearance; C_{max}, maximum plasma concentration; CYP, cytochrome P450; F_u, fraction unbound; GMR, geometric mean ratio; HI, hepatic impairment; LC-MS/MS, liquid chromatography with tandem mass spectrometry; m/z, mass-to-charge ratio; MELD, model of end-stage liver disease; MPR, metabolite-to-parent ratios; MRM, multiple reaction monitoring; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; t_{max}, time to reach maximum plasma concentration.

Primary Laboratories of Origin: Orlando Clinical Research Center, Orlando, Florida, USA and Clinical Pharmacology of Miami, LLC., Evolution Research Group, Miami, Florida, USA.

1 | INTRODUCTION

Insomnia is often treated pharmacologically, most commonly with sedative-hypnotic drugs including benzodiazepines and the nonbenzodiazepine "Z" drugs or with sedating antidepressants.[1] Lemborexant (Dayvigo®) is a novel dual orexin receptor antagonist[2,3] that has been approved by the US Food and Drug Administration, the Pharmaceuticals and Medical Devices Agency in Japan, and the Health Products and Food Branch of Health Canada for the treatment of adults with insomnia.[4] The efficacy and safety of lemborexant for insomnia disorder have been examined in two phase III pivotal studies, Study E2006-G000-304 (Study 304; SUNRISE-1; NCT02783729[5]) and Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820[6]). In Study 304, subjects treated with lemborexant experienced greater benefit on objective and subjective measures of sleep onset and sleep maintenance over 1 month compared with subjects treated with placebo. In the longer-term Study 303, subjects treated with lemborexant experienced greater benefit on subjective measures of sleep onset and sleep maintenance over 6 months than subjects receiving placebo.[6] In both studies, lemborexant was well tolerated and adverse events were generally mild to moderate in severity.[5,6]

Appropriate dosing of any drug for individual patients is essential to balance efficacy and safety. Hepatic disease can alter the pharmacokinetic (PK) properties of a drug; therefore, it is important to explore the potential impact of hepatic impairment (HI) to determine if a dose adjustment is needed.[7,8] US Food and Drug Administration regulatory guidelines recommend that the effect of HI on the PK of a drug and its main metabolites should be evaluated if hepatic metabolism accounts for at least 20% of elimination of the drug.[7] Prescribing information for the "Z" drugs zolpidem and zaleplon, which are commonly prescribed to treat insomnia, recommend dose limitations in patients with mild to moderate HI.[9,10]

In vitro drug metabolism studies (unpublished data on file, Eisai Inc., Woodcliff Lake, New Jersey, USA) and an open-label, phase I, [^{14}C]lemborexant human mass balance study (Study E2006-A001-007 [Study 007], NCT02046213[11]) have found that lemborexant is primarily metabolized via the cytochrome P450 (CYP)3A pathway. These results were consistent with outcomes from two clinical drug–drug interaction studies (Study E2006-A001-004 [Study 004], NCT02085967 and Study E2006-A001-012 [Study 012], NCT03451110) with CYP3A inhibitors (itraconazole and fluconazole) and inducer (rifampicin).[12] In support of this, in Study 007, approximately 57.4% of administered radioactivity was recovered in feces and 13% of the administered dose was recovered unchanged in feces.[11] The major metabolic pathways of lemborexant were oxidation of the dimethylpyrimidine moiety of lemborexant to the M4, M9, and M10 metabolites and subsequent further oxidation or glucuronidation or both.[11] Metabolites of lemborexant were also found to exhibit low pharmacological and toxicological activity.[11] One in vitro study demonstrated that lemborexant metabolites (M4, M9, and M10) are also metabolized via CYP3A as the primary pathway (unpublished data on file, Eisai Inc.).

This phase I study (E2006-A001-104; NCT03440424) evaluated the effects of mild and moderate HI on the PK of lemborexant following single oral dose administration. Of the metabolites formed, the highest relative exposures in humans were attributed to M4, M9, and M10, but only M10 was identified as the major circulating metabolite in humans (>10% of total drug-related exposure[11]); hence, the PK of these metabolites are summarized in addition to lemborexant.

2 | MATERIALS AND METHODS

This was a multicenter, single-dose, open-label, parallel-group study conducted between January 26, 2018 and April 23, 2018 at two sites in the United States. 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 and the Declaration of Helsinki. Informed consent was obtained in writing from all subjects prior to any screening procedures.

2.1 | Subjects

Subjects were males and females 18–79 years of age with body mass index (BMI) between 18 and 40 kg/m^2 who were either nonsmokers or smokers who smoked ≤20 cigarettes per day. Exclusion criteria included women who were pregnant or breastfeeding, positive HIV status, engagement in strenuous activities within the past 2 weeks (strenuous exercise can result in a short-term elevation of liver enzymes[13]), prolonged QT/QTc interval, major surgery within 4 weeks, or history of any abdominal surgery that could affect the PK of lemborexant.

Subjects with mild HI met criteria for Child–Pugh class A and subjects with moderate HI met criteria for Child–Pugh class B.[14] Exclusion criteria for subjects with HI included significant acute medical illness, esophageal or gastric variceal bleeding within the past 6 months, spontaneous bacterial peritonitis within 3 months, primarily cholestatic liver disease, autoimmune liver disease, hepatoma or metastatic liver disease, active alcoholic hepatitis, significant gastrointestinal disease, severe ascites or edema, significant bleeding diathesis, creatinine clearance <60 ml/min, and drug or alcohol dependency or abuse within 4 weeks of screening. Based on drug–drug interaction studies with strong CYP3A inhibitors,[12] severe HI was anticipated to have a strong effect on lemborexant exposure. Therefore, only subjects with mild and moderate HI were included in this study.

Subjects with HI were permitted to receive concomitant standard therapy approved by the Medical Monitor for diseases related to cirrhosis with the following restrictions applied: All such standard

concomitant medications remained unchanged for at least 14 days before dosing with study drug and for the duration of the study; standard concomitant medication was not administered at least 4 hours before or after study drug administration on Day 1; standard concomitant therapy of any agent known to induce or inhibit drug-metabolizing enzymes was prohibited within 2 weeks before dosing and until study discharge.

Healthy control subjects with normal hepatic function were matched to subjects with mild or moderate HI with regard to age (±10 years), sex, and BMI (± 20%) and as determined by no clinically significant deviation from normal in medical history, physical examination, ECG, and clinical laboratory determinations. Additional exclusion criteria for healthy control subjects included active liver disease or acute liver injury, clinically significant illness within 4 weeks, history of drug or alcohol use disorder within 2 years, and recent use of prescription or over-the-counter drugs.

A complete description of study enrollment criteria for all cohorts is available on clinicaltrials.gov.

2.2 | Study design and treatment

All eligible subjects received a single oral dose of lemborexant 10 mg in the morning of Day 1 after an overnight fast. Subjects remained in the clinic until Day 8 and returned for additional PK sampling through Day 14. During the study, subjects were prohibited from having foods, beverages, or supplements (e.g., St. John's wort) that are known to affect the CYP3A enzyme or transporters (e.g., grapefruit-containing foods or vegetables from the mustard-green family).

2.3 | Bioanalytical methods and PK assessments

For PK assessments of lemborexant and its metabolites, blood samples (4 ml each) were collected predose and up to 312 hours (13 days) postdose. Blood samples (12 ml each) were also collected for plasma protein–binding assessments of lemborexant at 1 and 24 hours postdose. Sodium heparin was used as the anticoagulant for all blood samples.

Total plasma concentrations of lemborexant and its metabolites, M4, M9, and M10, were measured via validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Lemborexant and its metabolites were extracted from 100 µl of human plasma with a liquid–liquid extraction technique. LC-MS/MS analyses were carried out with a Sciex (Framingham, Massachusetts, USA) API-5500 Triple Quad mass spectrometer coupled with a Shimadzu (Kyoto, Japan) liquid chromatography system equipped with a Phenomenex Kinetex (Torrance, California, USA) 5 µm XB-C18 100A 250 × 4.6 mm liquid chromatography column. The mass spectrometer was operated in positive electrospray ionization and multiple reaction monitoring (MRM) modes. As previously described, the MRM transition was mass-to-charge ratio (*m/z*) 411.0 → 287.1 for lemborexant and (*m/z*) 414.0 → 290.1 for the deuterated internal standard lemborexant-d_3.[15] The MRM transition was (*m/z*) 427.0 → 287.1 for M4, M9, and M10 and 414.0 → 290.1 for M4-d_3, M9-d_3, and M10-d_3. For all analytes, the lower limit of quantitation was 0.0500 ng/ml; the calibration curve ranged from 0.0500 to 50.0 ng/ml. The inter-day and intra-day precision and accuracy were <14.7% across all analytes and incurred sample reanalysis passed acceptance criteria.[16] Human plasma samples were stable for up to 34 months at −70°C. For determination of the plasma protein unbound fraction (f_u), a similar validated LC-MS/MS method was employed after equilibrium dialysis of plasma samples against phosphate-buffered saline.

PK parameters of lemborexant and its metabolites 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 PK parameters included apparent body clearance (CL/F), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$), and AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$).

2.4 | Nonparametric simulation model of single-dose PK data to steady state

To explore further the single-dose findings under steady-state conditions, plasma concentration-time profiles at steady state were projected by nonparametric simulations of single-dose plasma concentration-time profiles from this study using Phoenix WinNonLin (Phoenix 64, version 7.0 by Pharsight). Simulations were conducted for all subjects with mild and moderate HI and for subjects with normal hepatic function. Systemic exposure ($AUC_{0\text{-}24\ h}$) was calculated based on the projected steady-state profiles. The geometric mean ratio (GMR) for $AUC_{0\text{-}24\ h}$ of lemborexant was calculated for mild HI versus normal hepatic function and moderate HI versus normal hepatic function.

2.5 | Safety assessments

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

2.6 | Statistical analyses

A sample size of eight subjects per each cohort (mild and moderate HI) was based on recommendations in regulatory guidelines for the minimum number of subjects to be dosed in a moderate HI cohort.[7] Additionally, from single-dose studies of lemborexant

10 mg (unpublished data on file, Eisai Inc.), the pooled between-subject standard deviations of logarithmically transformed C_{max} and $AUC_{0\text{-inf}}$ of lemborexant were 0.334 ng/ml and 0.391 h·ng/ml, respectively. With a sample size of eight subjects in each HI category and eight matched healthy control subjects with normal hepatic function, a two-sided 90% confidence interval (CI) for the ratio for $AUC_{0\text{-inf}}$ was expected to extend 0.322 log units from the observed mean difference on the log scale.

Demographics and baseline characteristics for each subject group were summarized using descriptive statistics.

A general linear model of logarithmically transformed values with hepatic function class as a fixed effect was used to estimate the GMR and two-sided 90% CIs of PK parameters.

Safety data were summarized by subject group using descriptive statistics.

2.7 | 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,[17] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[18]

3 | RESULTS

3.1 | Subject disposition and characteristics

Twenty-eight subjects were screened, of whom 24 subjects entered and completed the study. Of the four subjects who failed screening, one did not meet entry criteria, two withdrew consent, and the appropriate cohort had already been filled in one case. The 24 subjects formed both the PK Analysis Set and the Safety Analysis Set. Eight subjects were enrolled in each of three groups: healthy control subjects with normal hepatic function, subjects with mild HI, and subjects with moderate HI. Each of the two study sites enrolled four healthy control subjects, four subjects with mild HI, and four subjects with moderate HI.

Patient demographics were generally similar among the mild HI, moderate HI, and healthy control subjects (Table 1), except that moderate HI subjects were somewhat older, were less likely to be of Hispanic or Latino ethnicity, and had higher BMI.

Use of prior medication was comparable in the two groups with HI, and no prior medication use was reported among the healthy control subjects with normal hepatic function. One subject with normal hepatic function was prescribed 500 mg of oral paracetamol once for a mild treatment-emergent headache on Day 1. All other concomitant medications were ongoing at the time of subject enrollment, were permitted per protocol, and were not considered to have affected the safety or PK assessments.

3.2 | Pharmacokinetic results: lemborexant

Mean lemborexant plasma concentrations were higher among subjects with mild and moderate HI compared with subjects with normal hepatic function (Figure 1). The C_{max} of lemborexant was higher by approximately 58% in mild HI subjects and approximately 22% in moderate HI subjects compared with subjects with normal hepatic function (Table 2). In addition, $AUC_{0\text{-inf}}$ was higher by approximately 25% in mild HI subjects and approximately 54% in moderate HI subjects compared with subjects with normal hepatic function (Table 2). The number of subjects in calculations of $AUC_{0\text{-inf}}$ was seven for mild HI and six for moderate HI. Subjects were excluded when the extrapolated portion of $AUC_{0\text{-inf}}$ was greater than 20% because they did not meet the criteria to be included in the summary statistics. Intersubject variability (%CV) in lemborexant exposure measured by $AUC_{0\text{-inf}}$ was higher in mild HI subjects compared with moderate HI subjects or subjects with normal hepatic function (Table 2).

TABLE 1 Summary of patient demographics and baseline characteristics

Parameter	Normal hepatic function (n = 8)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)	Overall (n = 24)
Age, mean (S.D.), y	56.8 (8.3)	57.0 (10.5)	61.4 (5.7)	58.4 (8.3)
Sex, *n* (%)				
Female	3 (37.5)	2 (25.0)	2 (25.0)	7 (29.2)
Male	5 (62.5)	6 (75.0)	6 (75.0)	17 (70.8)
White race, *n* (%)	8 (100.0)	8 (100.0)	8 (100.0)	24 (100.0)
Hispanic or Latino ethnicity, *n* (%)	5 (62.5)	5 (62.5)	2 (25.0)	12 (50.0)
Weight, mean (S.D.), kg	80.56 (10.40)	83.58 (18.73)	102.41 (17.40)	88.85 (18.15)
Height, mean (S.D.), cm	167.28 (8.32)	170.94 (8.80)	172.03 (11.32)	170.08 (9.38)
BMI, mean (S.D.), kg/m^2	28.75 (2.84)	28.54 (5.77)	34.33 (1.98)	30.54 (4.61)

Abbreviation: BMI, body mass index.

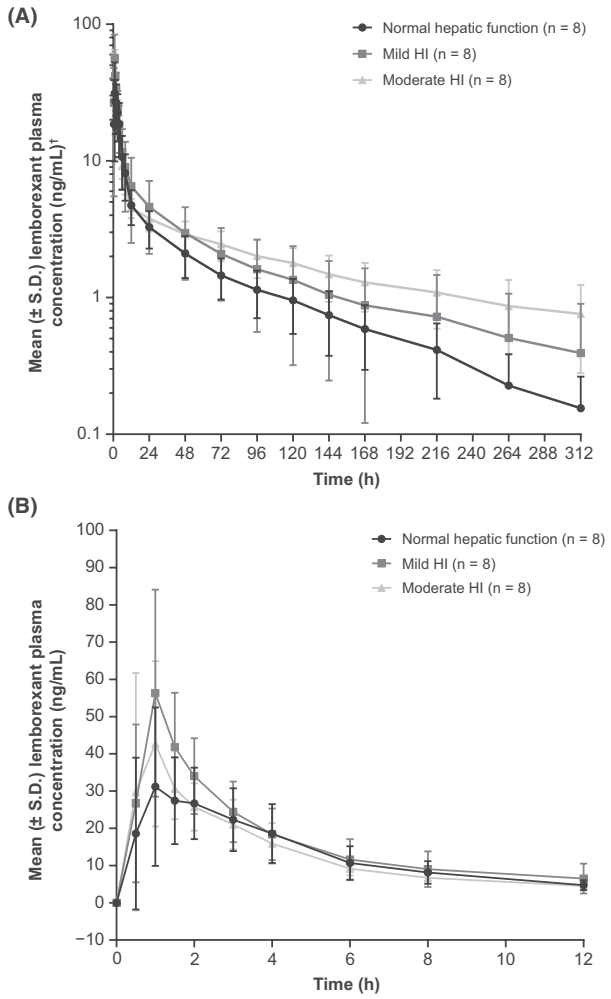

FIGURE 1 Plasma lemborexant concentration-time profiles after administration of a single dose of lemborexant 10 mg to healthy control subjects with normal hepatic function, subjects with mild hepatic impairment (HI), and subjects with moderate HI: (A) semi-logarithmic scale up to 312 h (B) linear scale up to 12 h. †Negative error bars where missing are due to the use of a logarithmic *y*-axis scale

In the analysis of GMRs of exposure parameters for subjects with mild or moderate HI compared with subjects with normal hepatic function (Figure 2), an approximate 1.25- to 1.5-fold increase in lemborexant C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ for subjects with mild or moderate HI compared with subjects with normal hepatic function was observed. In general, the effects seen with HI subjects were small; however, moderate HI had a slightly larger effect on lemborexant exposure (AUC) than mild HI (Figure 2).

Median t_{max} of lemborexant was similar in all groups (Table 2), and a longer geometric mean terminal half-life ($t_{1/2}$) was observed in subjects with mild and moderate HI compared with subjects with normal hepatic function (Table 2). CL/F was lower by 20% and 35% in mild and moderate HI subjects, respectively, versus subjects with normal hepatic function (Table 2). Similar mean plasma concentrations of lemborexant f_u were seen across groups, indicating that HI does not affect protein binding of lemborexant (Table 2).

3.3 | Nonparametric simulation model of lemborexant at steady state

To further identify the relative difference between the effect of mild and moderate HI on lemborexant exposure, steady-state simulations were conducted in all subjects. As $AUC_{0\text{-}inf}$ was not reportable in all mild and moderate HI subjects (Table 2), further simulations at steady state were conducted to estimate $AUC_{0\text{-}24\ h}$ in all subjects. The impact on exposure (C_{max} and AUC) at steady state was slightly higher than that observed following a single dose. Under simulated steady-state dosing conditions, C_{max} values were higher for mild and moderate HI subjects compared with normal subjects. $AUC_{0\text{-}24\ h}$ was approximately 20% higher with moderate HI than with mild HI (Table 3). In addition, $AUC_{0\text{-}24\ h}$ was increased in subjects with moderate HI (ratio for moderate: normal of 1.69) and mild HI (ratio for mild: normal of 1.45) compared with healthy control subjects at steady state. Median t_{max} was similar across groups (Table 3). Overall, the steady-state model data support the PK findings following a single dose, with both demonstrating increased lemborexant exposure with moderate HI compared with mild HI.

3.4 | Pharmacokinetic results: Lemborexant metabolites

For M4, M9, and M10, the geometric mean C_{max} was generally lower in subjects with mild or moderate HI compared with healthy control subjects, but no apparent differences were observed in the median t_{max} of each metabolite across cohorts (Table 2). In general, exposure ($AUC_{0\text{-}inf}$) to M4, M9, and M10 was comparable across cohorts, and no consistent trends were observed for a change in metabolite exposure with HI. Although the geometric mean metabolite-to-parent ratios (MPR) of $AUC_{0\text{-}inf}$ were slightly decreased with HI relative to healthy control subjects, the MPR values were still comparable across cohorts (Table 2).

There was no statistically significant relationship between C_{max} or $AUC_{0\text{-}inf}$ of M4, M9, or M10 and Child–Pugh score. Statistically significant decreases in C_{max} of M4 (R^2 = 0.208, p = 0.025), M9 (R^2 = 0.220, p = 0.021), and M10 (R^2 = 0.170, p = 0.045) were observed with increasing MELD score. However, there was no apparent relationship between $AUC_{0\text{-}inf}$ of M4, M9, or M10 and MELD score. There was no relationship between C_{max} of M4, M9, or M10 and serum albumin. There was also no relationship between $AUC_{0\text{-}inf}$ of M4 or M10 and serum albumin; however, a statistically significant decrease (R^2 = 0.323, p = 0.009) in M9 $AUC_{0\text{-}inf}$ was observed with increasing serum albumin. There was no statistically significant relationship between C_{max} or $AUC_{0\text{-}inf}$ of M4, M9, or M10 and any of the following measures: total bilirubin, prothrombin time, serum creatinine, ALT, or AST.

Across the three metabolites, in subjects with mild or moderate HI, GMRs for C_{max} (mild or moderate HI versus normal hepatic function) ranged from 65.7% to 97.0%, and GMRs for $AUC_{0\text{-}inf}$ ranged from 78.5% to 117.0% (Figure S1).

TABLE 2 Geometric mean (%CV) of PK parameters of lemborexant and lemborexant metabolites M4, M9, and M10 after administration of lemborexant 10 mg to healthy control subjects with normal hepatic function or subjects with mild or moderate hepatic impairment

Parameter	Normal hepatic function (n = 8)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)
Lemborexant			
t_{max}, h[a]	1.25 (0.50–4.00)	1.00 (0.50–1.50)	1.00 (0.50–3.00)
C_{max}, ng/ml	39.8 (31.1)	62.9 (34.9)	48.7 (37.7)
$AUC_{0\text{-inf}}$, h·ng/ml	453 (33.9)	567 (52.0)[b]	696 (34.6)[c]
CL/F, L/h	22.1 (33.9)	17.6 (52.0)[b]	14.4 (34.6)[c]
F_u[d]	0.060 (0.009)	0.064 (0.009)	0.065 (0.007)
Vz/F, L	2130 (30.1)	1880 (72.7)[b]	2170 (13.5)[c]
$t_{1/2}$, h	67.0 (26.9)	73.7 (43.6)[b]	105 (28.5)[c]
M4			
t_{max}, h[a]	2.00 (1.00–4.00)	1.75 (1.00–4.00)	1.75 (1.00–4.00)
C_{max}, ng/ml	7.97 (33.0)	7.73 (36.4)	5.74 (46.7)
$AUC_{0\text{-inf}}$, h·ng/ml	191 (31.6)	220 (50.3)[c]	223 (21.3)[c]
MPR $AUC_{0\text{-inf}}$	0.405 (11.5)	0.343 (2.90)[c]	0.289 (23.4)[e]
M9			
t_{max}, h[a]	1.50 (1.00–4.00)	1.25 (1.00–3.00)	1.25 (1.00–4.00)
C_{max}, ng/ml	5.33 (28.9)	4.49 (45.1)	3.50 (46.4)
$AUC_{0\text{-inf}}$, h·ng/ml	92.5 (23.5)	72.6 (34.7)[b]	108 (21.6)[c]
MPR $AUC_{0\text{-inf}}$	0.198 (22.0)[b]	0.123 (19.0)[b]	0.144 (17.4)[e]
M10			
t_{max}, h[a]	4.00 (4.00–24.00)	4.00 (2.00–24.00)	3.00 (1.00–4.00)
C_{max}, ng/ml	3.71 (34.8)	3.52 (44.4)	2.84 (38.4)
$AUC_{0\text{-inf}}$, h·ng/ml	320 (41.9)	304 (27.7)[c]	332 (17.9)[e]
MPR $AUC_{0\text{-inf}}$	0.680 (18.9)	0.600 (15.3)[c]	0.502 (20.4)[e]

Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 extrapolated to infinity; CL/F, apparent body clearance; C_{max}, maximum plasma concentration; F_u, fraction unbound; MPR $AUC_{0\text{-inf}}$, ratio of $AUC_{0\text{-inf}}$ of individual metabolite to $AUC_{0\text{-inf}}$ of lemborexant, corrected for molecular weights; PK, pharmacokinetic; $t_{1/2}$, terminal elimination half-life; t_{max}, time to reach maximum plasma concentration; Vz/F, apparent volume of distribution.

[a]Presented as median (range).

[b]n = 7.

[c]n = 6.

[d]Reported as arithmetic mean (S.D.); 1 and 24 h postdose data were averaged.

[e]n = 5.

3.5 | Safety

Seven subjects (87.5%) with normal hepatic function, seven subjects with mild HI (87.5%), and six subjects with moderate HI (75.0%) experienced TEAEs (Table S1). All TEAEs were mild in severity, and none led to a subject discontinuation. No serious TEAEs were reported.

Somnolence, the most common TEAE, was experienced by seven subjects with normal hepatic function, seven with mild HI, and five with moderate HI. This finding is not unexpected given the daytime dosing with a sleep-promoting drug. The remaining TEAEs reported were chills, dry mouth, and headache, each experienced by one subject with moderate HI. No TEAEs were related to clinically significant abnormalities in laboratory tests, ECGs, vital signs, or physical examinations.

4 | DISCUSSION

The present study was conducted to assess lemborexant PK in subjects with mild or moderate HI, as recommended by regulatory guidelines,[7] following a single dose of lemborexant 10 mg, the highest dose administered in phase III clinical testing.[5,6] This study found that, in mild HI and moderate HI subjects, lemborexant t_{max} was unaltered, C_{max} was increased ~1.6-fold and ~1.2-fold, and $AUC_{0\text{-inf}}$ was increased 1.25-fold and ~1.5-fold, respectively, compared with healthy control subjects with normal hepatic function. In addition, total CL/F of lemborexant was decreased by 20% in mild HI subjects and 35% in moderate HI subjects as compared with healthy control subjects.

In general, the PK of lemborexant and its metabolites M4, M9, and M10 were comparable between the mild and moderate

HI cohorts. However, in the mild HI cohort, C_{max} was higher, while $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were lower compared with the moderate HI cohort. C_{max} occurs during the target pharmacologic time period of the drug, which coincides with the onset of drug effect. AUC represents overall exposure over time, including next-day overall exposure for a drug taken at night. Thus, although C_{max} was elevated approximately 1.6-fold in mild HI subjects relative to healthy control subjects, the 1.25-fold increase in overall exposure ($AUC_{0\text{-}inf}$) in mild HI subjects was lower than the C_{max}-related difference and similar to the healthy control cohort. In contrast, the approximately 1.5-fold higher $AUC_{0\text{-}inf}$ for moderate HI compared with healthy control subjects corresponds to higher exposure during the daytime than that observed for mild HI. To further strengthen the single-dose data and better understand the differences in C_{max} and AUC across cohorts, simulations at steady state were conducted. These analyses showed that the effect observed with mild HI on lemborexant exposure was lower than that observed with moderate HI, consistent with the single-dose data. Therefore, based on the observations of increased exposure (AUC) in moderate HI subjects, patients with moderate HI should not exceed the lemborexant 5 mg dose. This dose adjustment is supported by the linear PK profile of lemborexant over a wide dose range (up to 25 mg), as demonstrated in Phase 1 clinical studies.[15]

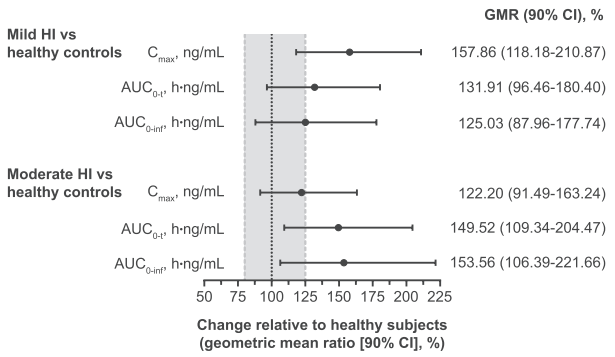

FIGURE 2 Geometric mean ratios (GMRs) (90% confidence intervals [CIs])[†] of lemborexant for subjects with mild or moderate hepatic impairment (HI) versus healthy control subjects with normal hepatic function. The vertical dashed lines at 80% and 125% represent the US Food and Drug Administration *no effect* boundary.[7†]Based on least squares mean of log-transformed parameter values. $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to time of last quantifiable concentration; C_{max}, maximum plasma concentration

The geometric mean $t_{1/2}$ of lemborexant was generally higher in moderate HI subjects compared with healthy control subjects. It is important to note that the measure $t_{1/2}$ does not take into account accumulation and disposition of the drug. Since lemborexant presents a multicompartment distribution, effective half-life ($t_{1/2,eff}$) may be a more clinically meaningful measure than $t_{1/2}$.[15] Landry and colleagues reported the mean geometric $t_{1/2,eff}$ for lemborexant 10 mg to be 19 hours.[15] For the present study, $t_{1/2,eff}$ was not evaluable as this study is based on a single dose of lemborexant.

In addition, the effect of HI on protein binding of lemborexant was evaluated by measuring the unbound drug fraction in plasma. The f_u of lemborexant was similar in subjects with mild or moderate HI and healthy control subjects, indicating that HI does not affect protein binding of lemborexant. In this study, lemborexant was metabolized to M4, M9, and M10. These results are in agreement with results previously observed in in vitro drug metabolism studies and Study 007, which reported that M10 accounted for greater than 10% of total plasma exposure.[11] HI had no effect on the MPRs for M4, M9, and M10.

In this study, lemborexant was well tolerated among subjects with mild or moderate HI and among healthy control subjects. All TEAEs reported during the study were consistent with the known safety profile of lemborexant and were mild in severity.[5,6] The frequent occurrence of somnolence in this study was not unexpected, given that subjects received a morning dosing of a sleep-promoting drug. The exclusion of subjects with extrapolation greater than 20% from the $AUC_{0\text{-}inf}$ calculations can be considered a limitation.

In conclusion, the effect of mild HI on lemborexant exposure was considered small; therefore, a dose adjustment is not warranted in patients with mild HI. However, moderate HI increased overall lemborexant exposure, thereby warranting a maximum dose recommendation of no more than lemborexant 5 mg once-nightly in patients with moderate HI.[4]

TABLE 3 Geometric mean (%CV) of PK parameters after administration of lemborexant 10 mg at simulated steady state for healthy control subjects with normal hepatic function or subjects with mild or moderate hepatic impairment

Parameter	Normal hepatic function (n = 8)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)
Lemborexant			
t_{max}, h[a]	1.57 (1.04–3.13)	1.04 (1.04–2.09)	1.04 (1.04–3.13)
C_{max}, ng/ml	49.9 (22.4)	79.4 (31.5)	70.2 (25.2)
$AUC_{0\text{-}24\ h}$, h·ng/ml	456 (33.5)	659 (65.1)	772 (35.0)
Ratio based on $AUC_{0\text{-}24\ h}$		Mild:Normal 1.45	Moderate:Normal 1.69

Abbreviations: $AUC_{0\text{-}24\ h}$, area under the concentration-time curve from time 0 to 24 h postdose; C_{max}, maximum plasma concentration; PK, pharmacokinetic; t_{max}, time to reach maximum plasma concentration.

[a]Presented as median (range).

ETHICS STATEMENT

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.

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CONFLICTS OF INTEREST

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

AUTHOR 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.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

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

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