Revision History
Previous Version: v1.0
Current Version: v2.0
Date of Latest Revision: 28 Feb 2018 (revised per Amendment 01)

Change	Rationale	Affected Protocol Sections
Remove alpha-1-glycoprotein (AGP) testing.	Test is not required and was included in error.	• Section 4 • Section 9.5.1.5.3 (Table 3) • Section 9.5.2.1 (Table 4)
Add creatinine testing	Test is required and was not included in error.	• Section 9.5.1.5.3 (Table 3) • Section 9.5.2.1 (Table 4)
Added Adjudication Committee information	Correction	• Synopsis • Section 9.2
Revised serious adverse event (SAE) reporting time period	To comply with internal and regulatory standards	• Section 9.5.4.1

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2006-A001-104
Study Protocol Title:	An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant (E2006) and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA
Investigational Product Name:	E2006/Lemborexant
Indication:	Not applicable
Phase:	1
Approval Date:	V1.0 29 Dec 2017 (original protocol) V2.0 28 Feb 2018 (Amendment 01)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E2006/lemborexant
Name of Active Ingredient (1R,2S)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide
Study Protocol Title An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant (E2006) and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects
Investigators Thomas C. Marbury, MD (Orlando Clinical Research Center) Kenneth C. Lasseter, MD (Clinical Pharmacology of Miami, LLC., Evolution Research Group)
Sites Up to 4 sites
Study Period The total study duration from the first subject enrolled (screened) to the last subject's last visit/last assessment will be approximately 17 weeks.
Phase of Development Phase 1
Objectives <u>Primary Objective</u> The primary objective is to assess the effect of mild and moderate hepatic impairment on the pharmacokinetics (PK) of lemborexant after a single dose administration. <u>Secondary Objectives</u> • To evaluate the effects of hepatic impairment on the PK of lemborexant metabolites M4, M9, and M10. • To evaluate the relationship between the PK parameters of lemborexant and its metabolites and the Child-Pugh Classification score, serum albumin, total bilirubin, and prothrombin time. • To assess safety and tolerability of lemborexant following a single dose administration in subjects with mild and moderate hepatic impairment and in healthy subjects. <u>Exploratory Objectives</u> • To explore the relationship between the PK parameters of lemborexant and its metabolites and the model of end stage liver disease (MELD) score.
Study Design This is a multicenter, single dose, open-label, parallel-group study in subjects with mild and moderate hepatic impairment and matched (with regard to age [±10 years], sex, and body mass index [BMI, ±20%]) healthy control subjects. The study will enroll a total of 24 subjects, including 16 subjects with impaired hepatic function; 8 subjects each in Child-Pugh class A (mild) and B (moderate). Approximately 8 healthy subjects will be dosed as one control group to match (1:1) to the subjects with hepatic impairment in each Child-Pugh class with regard to age, sex, and BMI. The study will consist of 2 phases: Prerandomization and Treatment. The Prerandomization Phase will include 2 study periods; Screening and Baseline (Day -1). The subjects will be admitted to the clinical facility on Day -1, remain confined to the clinic until Day 8, and then return to the clinical facility for additional PK

sampling as outpatients until Day 14. In the event of early discontinuation of the subjects, the subjects with Child Pugh Class A and B (Cohorts A and B) and the matched controls (Cohort C) may be replaced.

On Day 1, the subjects will be administered a single 10-mg dose of lemborexant with approximately 240 mL of water in the morning after an overnight fast. The blood samples for PK assessments will be collected at prespecified intervals up to 312 hours postdose administration. The subjects will be discharged on Day 14 of the study. In addition, the blood samples for plasma protein binding assessments of lemborexant will be collected from each subject at 2 time points; approximately 1 hour and 24 hours postdose.

Adjudication Committee (revised per Amendment 01)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [standardized MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia, [faintness] and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the serious adverse event (SAE) form for any of the above events considered serious.

Number of Subjects

A total of 24 subjects will be enrolled in the following 3 cohorts:

Cohort A: 8 subjects with mild hepatic impairment (Child Pugh Class A)

Cohort B: 8 subjects with moderate hepatic impairment (Child Pugh Class B)

Cohort C: At least 8 healthy subjects (control) matched to subjects in Cohorts A and B

Inclusion Criteria

Inclusion Criteria for All Subjects

Subjects who meet all of the following inclusion criteria will be eligible for participation in the study.

1. Male or female subjects, ages 18 to 79, inclusive, at the time of informed consent.
2. BMI between 18 and 40 kg/m^2, inclusive, at Screening.
3. Voluntary agreement to provide written informed consent, and the willingness and ability to comply with all aspects of the protocol.
4. Nonsmokers or smokers who smoke 20 cigarettes or less per day.
5. For Cohorts A and B: stable (without any change in disease status for at least 60 days prior to study screening) hepatic impairment conforming to Child-Pugh classification A or B, respectively (see the following tables) and documented by medical history and a physical examination.
6. For Cohort C: healthy subjects matched to subjects with hepatic impairment 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, electrocardiogram (ECG), and clinical laboratory determinations.

Criteria for Child-Pugh Classification			
	Points Scored for Observed Findings		
Clinical or Biochemical Assessments	**1**	**2**	**3**
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
Bilirubin (mg/dL)	<2	2 – 3	>3
PT (seconds prolonged)	<4	4 – 6	>6
or INR	<1.7	1.7 – 2.3	>2.3

Ascites	None	Mild/Moderate (diuretic-responsive)	Tense (diuretic-refractory)
Encephalopathy[a]	None	1 or 2 (or precipitant-induced)	3 or 4 (chronic)

cps=cycle per second; INR=international normalized ratio; PT=prothrombin time

a: Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram; Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, and 5 cps waves; Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves; Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Child-Pugh Classification Scoring	
Total Points	**Child-Pugh Class**
5 – 6	A
7 – 9	B

Exclusion Criteria

Exclusion Criteria for All Subjects

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the dose of study drug.
2. Females of childbearing potential who did not use a highly effective method of contraception (as described below) within 28 days before study entry, or who do not agree to use an approved method of contraception from 28 days before study entry, throughout the entire study period, and for 28 days after study drug discontinuation. Approved (highly effective) methods of contraception for this study include at least one of the following:
   - Total abstinence (if it is their preferred and usual lifestyle)
   - An intrauterine device or intrauterine hormone-releasing system (IUS)
   - A double-barrier method of contraception such as condom plus diaphragm with spermicide
   - A contraceptive implant
   - An oral contraceptive (with additional barrier method). Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.
   - Have a vasectomized partner with confirmed azoospermia.

   (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
3. Known to be positive for human immunodeficiency virus (HIV).
4. Currently enrolled in another clinical study or used any investigational drug or device within 4 weeks, or 5 times the half-life of the investigational drug (whichever is longer), preceding informed consent.
5. Receipt of blood products within 4 weeks, or donation of blood within 8 weeks, or donation of plasma within 1 week of dosing until study discharge.
6. Intake of herbal preparations containing St. John's Wort within 4 weeks prior to dosing until study discharge.
7. Intake of nutritional supplements (including herbal preparations), foods or beverages that may affect CYP3A enzyme (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens,

kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 1 week before dosing until study discharge.

8. Intake of beverages, food, or other products that contain caffeine from 24 hours before until 48 hours after dosing with lemborexant.
9. Engagement in strenuous exercise (eg, moving large bulky items, bodybuilding) within 2 weeks prior to check-in until study discharge.
10. History of clinically significant drug or food allergies, or is presently experiencing significant seasonal allergies.
11. A prolonged QT/QTc interval (QTc >480 ms) demonstrated on ECG at Screening or Baseline (Day -1).
12. Any major surgery within 4 weeks of study drug administration.
13. Any history of abdominal surgery that may affect PK of lemborexant (eg, hepatectomy, nephrectomy, digestive organ resection).
14. Inability to tolerate oral medication.
15. Inability to tolerate venous access and/or venipuncture.
16. Unwilling to abide by the study requirements, or in the opinion of the investigator, is not likely to complete the study.

Additional Exclusion Criteria for Hepatically Impaired Subjects (Cohorts A and B)

In addition to the Exclusion Criteria above for All Subjects, other standard exclusion criteria for subjects with hepatic impairment will be used. These include:

17. Any significant acute medical illness (such as new conditions or exacerbation of pre-existing conditions) within 8 weeks of dosing.
18. Medical conditions which are not adequately and stably controlled on stable doses of medications or which, in the clinical opinion of the Principal Investigator, may interfere with study procedures or subject safety within 4 weeks before dosing (eg, psychiatric disorders and disorders of the gastrointestinal tract, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or subjects who have a congenital abnormality in metabolism).
19. History of esophageal and gastric variceal bleeding within the past 6 months unless the subject has completed a course of endoscopic therapy with the appropriate documentation (eg, endoscopy report) of successful ablation of esophageal varices; subjects with esophageal varices may be included if not bleeding within the past 6 months or have been treated adequately by ablation therapy, as specified above.
20. Spontaneous bacterial peritonitis within 3 months of dosing.
21. Treatment with plasmapheresis within 6 months of dosing.
22. Primarily cholestatic liver diseases (eg, primary biliary cirrhosis or primary sclerosing cholangitis).
23. Current or recent (within 3 months prior to screening) history of significant gastrointestinal disease other than that secondary to hepatic impairment.
24. Autoimmune liver disease.
25. Active alcoholic hepatitis determined either clinically or by histology.
26. History of hepatoma or metastatic disease of the liver.
27. Presence of severe ascites or edema.
28. Presence of hepatopulmonary syndrome or hydrothorax, or hepatorenal syndrome.
29. Known significant bleeding diathesis that could preclude multiple venipunctures (INR >2.5).
30. Creatinine clearance <60 mL/min at Screening or Baseline as calculated using Cockroft and Gault Equation.
31. The subject's standard therapy/concomitant medication for diseases related to cirrhosis has not remained stable/unchanged for at least 14 days before the first dose of study drug.

32. History of drug or alcohol dependency or abuse within 4 weeks prior to Screening, or those who have a positive urine drug test or breath alcohol test at Screening or Baseline unless a prescribed medication for the underlying condition is the cause of the positive urine screen.

Additional Exclusion Criteria for Healthy Subjects (Cohort C)

In addition to the Exclusion Criteria for All Subjects, other standard exclusion criteria for healthy subjects in Phase 1 studies will be used. These include:

33. Presence of active liver disease, or acute liver injury, as indicated by (1) an abnormal liver function test, or (2) clinical or laboratory signs of active viral hepatitis (including B and C as demonstrated by positive serology at Screening).
34. Clinically significant illness, within 4 weeks prior to dosing, that requires medical treatment or may influence the outcome of the study; eg, psychiatric disorders and disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or subjects who have a congenital abnormality in metabolism.
35. Any abnormal finding based on physical examination, assessment of vital signs, ECG, or laboratory test results that require treatment or clinical follow-up based on the investigator's opinion.
36. History of drug or alcohol use disorder within the 2 years prior to Screening, or those who have a positive urine drug test or breathalyzer alcohol test at Screening or Baseline.
37. Use of any prescription drugs within 4 weeks prior to dosing until study discharge.
38. Intake of any over-the-counter (OTC) medications within 2 weeks prior to dosing until study discharge.

Study Treatment

Test drug: Lemborexant (E2006)

All subjects enrolled in the study will receive a single 10-mg dose (1 × 10 mg lemborexant tablet)

Comparator Drug: Not applicable

Duration of Treatment

The study duration per subject will be as follows:

Prerandomization Phase: Up to 21 days

Treatment Phase: 14 days

Concomitant Drug/Therapy/ Lifestyle Restrictions

For all subjects enrolled in the study, any medication or therapy administered during the study will be recorded. The following are prohibited for all subjects during the study:

- Smokers must not smoke more than 20 cigarettes per day.
- Nutritional supplements, juice, and herbal preparations or other foods or beverages that may affect the various drug metabolizing enzymes and transporters (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], and charbroiled meats) within 1 week before dosing until study discharge.
- Intake of beverages, food, or other products that contain caffeine from 24 hours before until 48 hours after dosing with lemborexant.
- Herbal preparations containing St. John's Wort within 4 weeks before dosing until study discharge.
- Engagement in strenuous exercise is prohibited within 2 weeks before check-in and until study discharge.

For healthy subjects, use of prescription drugs is prohibited from 4 weeks before dosing until study discharge. Intake of over-the-counter (OTC) medications is prohibited within 2 weeks or 5 half-lives (whichever is longer) before dosing until study discharge. A list of prohibited medications is located in the protocol appendices.

Subjects with hepatic impairment may receive standard therapy approved by Medical Monitor for diseases related to cirrhosis, and the identity, dose, and regimen of such concomitant drugs must be recorded in the

CRF. All such concomitant medications should remain unchanged for 14 days before dosing with study drug and for the duration of the study. Concomitant medication may not be administered 4 hours before or after study drug administration on Day 1. Additionally, concomitant therapy of any agent known to induce or inhibit drug metabolizing enzymes is prohibited within 2 weeks before dosing until study discharge.

A full list of prohibited concomitant medications is located in the protocol appendices.

Assessments

Efficacy Assessments

Not applicable.

Pharmacokinetic Assessments

Blood samples (4 mL each) for PK assessments of lemborexant and its metabolites (M4, M9, and M10) will be collected at predose (0 hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 264 and 312 hours postdose. In addition, blood samples (12 mL per time point) for protein binding of lemborexant and its metabolites (M4, M9 and M10) will be collected at 1 and 24 hours postdose.

Safety Assessments

Safety will be assessed by monitoring and documenting adverse events (AEs), ECGs, vital signs, physical examinations, and clinical laboratory tests (urinalysis, hematology, and blood chemistry). Blood samples will be collected at Baseline and again if AEs of infection occur, for investigation of suspected infective pathogens.

Bioanalytical Methods

Total plasma concentrations of lemborexant and its main metabolites (M4, M9, and M10) will be measured by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. The unbound concentrations of lemborexant and its main metabolites will also be measured using a similar validated LC-MS/MS method following equilibrium dialysis.

Statistical Methods

Study Endpoints

The endpoints include the following PK parameters derived by non-compartmental analysis using the plasma concentration-time data of lemborexant and its metabolites:

C_{max}	Maximum plasma concentration
t_{max}	Time to reach maximum plasma concentration
$AUC_{(0\text{-}t)}$	Area under plasma concentration vs. time curve from time = 0 to time of last quantifiable concentration
$AUC_{(0\text{-}inf)}$	Area under plasma concentration vs. time curve from time = 0 to infinity
$t_{1/2}$	Terminal phase plasma half-life
CL/F	Apparent total body clearance (for lemborexant only)
Vz/F	Apparent volume of distribution (for lemborexant only)
AUC Metabolite Ratio	Ratio of $AUC_{(0\text{-}inf)}$ of individual metabolite to $AUC_{(0\text{-}inf)}$ of lemborexant, corrected for molecular weights
fu	Plasma protein unbound fraction
AUCu	$AUC_{(0\text{-}inf)}$ values adjusted by unbound fraction in plasma (for lemborexant only)
CLu/F	Apparent clearance relative to the unbound plasma concentration

based on AUCu (for lemborexant only)

The C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ of lemborexant will be the primary PK endpoints. The rest of the parameters, including the PK parameters of the metabolites, will be secondary endpoints.

Analysis Sets

The Safety Analysis Set is the group of subjects who dosed with the test drug and had at least 1 postdose safety assessment.

The Pharmacokinetic Analysis Set is the group of subjects who had sufficient PK data to derive at least 1 PK parameter.

Efficacy Analyses

Not applicable.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual plasma concentration listings. The PK Analysis Set will be used for summaries of plasma concentrations and for analyses, summaries, and listings of PK parameters.

The effect of hepatic impairment on the PK of lemborexant, the primary PK parameters based on total C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ will be compared between the cohort of healthy normal controls and the cohorts of subjects with mild and moderate hepatic impairment as defined by Child-Pugh classes A or B. A general linear model of logarithmically transformed values with hepatic function class as a fixed effect will be utilized to estimate the geometric mean ratio (and two-sided 90% confidence intervals) of subjects with mild/normal and moderate/normal hepatic function. Similar statistical analyses will be conducted for the PK parameters of the metabolites and unbound lemborexant as secondary endpoints. Protein binding will be calculated for metabolites without any assessment of PK parameters.

Scatter plots of PK parameters of lemborexant and its metabolites versus Child-Pugh Score will be provided. The association between the primary PK parameters and Child-Pugh Score will be evaluated by regression analysis (the PK parameter as a dependent variable and Child-Pugh Score as an independent variable). Similar analyses will be performed for MELD score, serum albumin, total bilirubin, and PT. Additionally, association between the PK parameters and liver transaminase levels will be performed, if deemed necessary.

Summary statistics will be generated for each of the PK parameters for each Child-Pugh class and healthy controls.

Safety Analyses

An evaluation of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and ECGs.

Treatment-emergent adverse events (TEAEs) will be summarized for each Child-Pugh class and healthy controls. Descriptive summary statistics (eg, mean, standard deviation [SD], median, minimum, maximum for continuous variables, and number and percent for categorical variables) including shift tables of the laboratory, vital signs, ECG parameters. Changes from Baseline for the clinical laboratory, vital signs and ECG parameters will be evaluated for each Child-Pugh class and healthy controls by time point.

Interim Analyses

Not applicable.

Sample Size Rationale

A sample size of 8 subjects per each cohort of mild and moderate hepatic impairment, as defined by Child-Pugh classes A or B, is based on the recommendations in regulatory guidelines for a minimum number of subjects to be enrolled for moderate liver impairment cohort (FDA, 2003). Additionally, from single-dose studies of the 10-mg tablet (E2006-A001-004, E2006-A001-005, and E2006-A001-008), the pooled between-subject standard deviations of logarithmically transformed C_{max} and $AUC_{(0-inf)}$ of lemborexant were 0.334 and 0.391 respectively. With a sample size of 8 subjects in each Child-Pugh category and at least 8 matched controls, a 2-sided 90% confidence interval (CI) for the ratio for $AUC_{(0-inf)}$ will extend 0.322 from the observed mean difference on the log scale.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under plasma concentration vs. time curve
$AUC_{(0\text{-}8h)}$	area under plasma concentration vs. time curve from time = 0 to 8 hours postdose
$AUC_{(0\text{-}96h)}$	area under plasma concentration vs. time curve from time = 0 to 96 hours postdose
$AUC_{(0\text{-}t)}$	area under plasma concentration vs. time curve from time = 0 to time of last quantifiable concentration
AUC_{inf}	area under plasma concentration vs. time curve from time = 0 to infinity
AUCu	$AUC_{(0\text{-}inf)}$ values adjusted by unbound fraction in plasma
BA	bioavailability
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CA	competent authority
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLu/F	Apparent clearance relative to the unbound plasma concentration based on AUCu
C_{max}	maximum drug concentration
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
CSR	clinical study report
CYP	cytochrome P450
DORA	dual orexin receptor antagonist
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
fu	Plasma protein unbound fraction
GCP	Good Clinical Practice

HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISWRD	Irregular Sleep-Wake Rhythm Disorder
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LLT	lower level term
LNH	low-normal-high
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
MHRA	Medicines and Healthcare products Regulatory Agency
OTC	over-the-counter
P-gp	P-glycoprotein
PT	preferred term
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal phase plasma half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum drug concentration
US	United States
Vz/F	Apparent volume of distribution
WBC	white blood cell
WCT	Worldwide Clinical Trials

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and competent authority (CA) within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki revised version Fortaleza 2013)

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Federal Regulations, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to 4 investigational sites in the United States (US).

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are provided to the sites.

7 INTRODUCTION

7.1 Indication

Lemborexant (E2006) is part of the dual orexin receptor antagonist (DORA) class of drugs and it is being developed as a treatment of insomnia disorder and for Irregular Sleep-Wake

Rhythm Disorder (ISWRD). Phase 1 and 2 studies in the lemborexant clinical program have provided evidence for pharmacological efficacy at safe and well-tolerated doses.

7.1.1 Lemborexant

The proposed study is an open-label, parallel-group study to evaluate the pharmacokinetics (PK) of lemborexant and its metabolites in subjects with normal hepatic function and subjects with mild and moderate hepatic impairment.

7.1.1.1 Therapeutic Pathway

Lemborexant (E2006), a dual orexin receptor antagonist, is an Eisai in-house discovered and developed small molecule which inhibits orexin by binding competitively to two subtypes of orexin receptors (orexin receptor 1 and 2). In individuals with insomnia, it is possible that the orexin system, which regulates sleep and wakefulness, is not functioning normally. During normal periods of sleep, orexin system activity is suppressed, suggesting it is possible to purposefully counteract inappropriate wakefulness and facilitate the initiation and maintenance of sleep by interfering with orexin neurotransmission.

7.1.1.2 Clinical Experience With Lemborexant

To date, a total of 9 Phase 1 studies have been completed, with healthy subjects treated with either single or multiple once daily doses for 14 days, and subjects with insomnia disorder who were administered single doses of lemborexant. In addition, a Phase 2 dose-finding study in adult and elderly subjects with insomnia disorder demonstrated efficacy and safety over a dose range from 1 mg to 25 mg to enable lemborexant to proceed into Phase 3 studies. Relevant to the currently proposed study, the tolerability data from the first human study suggest that single doses up to 200 mg have been generally well tolerated in healthy adult subjects.

Following single oral dose administration, lemborexant generally exhibited linear PK within the dose range studied (1 mg to 200 mg), but at doses of 50 mg and above, the increase in the maximum drug concentration (C_{max}) was less than dose proportional. Lemborexant exhibits approximate dose proportional (based on C_{max} and the area under the plasma concentration versus time curve [AUC]) PK at steady state on Day 14 following multiple dose administrations between 2.5 mg and 75 mg of lemborexant administered once daily. Oral absorption of lemborexant was rapid with peak plasma concentration around 1 to 3 hours postdose. The terminal half-life was ~45 to 55 hours over a comparable dose range following single and multiple dose administration of lemborexant. Accumulation of lemborexant following multiple dosing was lower than predicted by terminal half-life, with mean C_{max} ranging from 1.21 to 2.39 and an area under the concentration-time curve from zero time to 96 hours postdose ($AUC_{[0\text{-}96h]}$) of 1.67 to 3.26 over the dose range. Based on the overall drug accumulation, effective half-life of lemborexant ranged from 16.9 to 39.3 hours over the dose range. Exposure ($AUC_{[0\text{-}96h]}$) of the main inactive metabolites (M4, M9, M10) relative to lemborexant was 19.9% to 57.5% following multiple dosing at 25 mg for 14 days. Additionally, lemborexant exposures were similar between healthy volunteers administered lemborexant in the morning compared to otherwise healthy subjects with primary insomnia

administered lemborexant in the evening, suggesting that the time of dosing does not affect the PK.

Based on in vitro data, lemborexant and its main metabolites (M4, M9, and M10) were metabolized via CYP3A as the primary pathway. Coadministration of a single oral dose of lemborexant 10 mg and oral itraconazole 200 mg administered once daily (QD) under steady state conditions in healthy volunteers resulted in a moderate interaction as evidenced by approximately 36% and 3.7-fold increases in lemborexant C_{max} and area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{[0\text{-}inf]}$), respectively; the effect on lemborexant exposure during the 8 hours postdose was weak, as the with mean C_{max} ranging from 1.21 to 2.39 and an area under the concentration-time curve from zero time to 8 hours postdose ($AUC_{[0\text{-}8h]}$) increased by approximately 1.75-fold. The terminal half-life of lemborexant was extended from ~54 hours (lemborexant treatment only) to 118 hours following coadministration of itraconazole. Exposure of the main metabolites of lemborexant, ie, M4, M9, and M10 decreased between 32 - 87% (C_{max}) whereas $AUC_{(0\text{-}inf)}$ remained unchanged (M4), increased 2.4-fold (M9) and decreased by approximately 37% (M10) compared with the administration of lemborexant alone. Terminal half-lives of the metabolites increased approximately 2- to 3- fold (terminal phase plasma half-life [$t_{1/2}$] of ~108 to 150 hours) compared to administration of lemborexant alone ($t_{1/2}$ ~48 to 53 hours). Coadministration of a single 10-mg oral dose of lemborexant and oral rifampin 600 mg QD at steady state resulted in decreases in lemborexant C_{max}, and $AUC_{(0\text{-}inf)}$ by approximately 92% and 97%, respectively, as compared with administration of lemborexant alone. In vitro data also showed lemborexant to exhibit some inhibitory potential on CYP3A and CYP2B6. The effects of steady state dosing of lemborexant (10 mg) on a combined single oral dose of midazolam (a sensitive CYP3A substrate, 2 mg) and bupropion (a sensitive 2B6 substrate, 75 mg) in healthy subjects showed no effect on the PK for midazolam but a weak effect on the PK of bupropion based on approximately ~50% decreased exposure (C_{max} and $AUC_{[0\text{-}inf]}$ for bupropion and the [S,S]-hydroxylated metabolite of bupropion). These findings showed that the observed PK for midazolam and bupropion in this study were similar to reported values in literature, which confirms that there were no apparent effects on the PK of either drug when coadministered (Heizmann, et al., 1983; Lai and Schroeder, 1983). In summary, these findings suggest that no clinically meaningful interaction can be expected when lemborexant is administered concomitantly with other sensitive CYP3A or CYP2B6 substrates. However, lemborexant exposure may considerably increase or decrease when coadministered with either a strong CPY3A inhibitor or inducer respectively.

Regulatory guidelines related to assessing PK in hepatic impaired subjects recommend that the effect of hepatic impairment on the PK of the drug and its main metabolites should be evaluated if hepatic metabolism accounts for at least 20% of elimination of the drug (FDA, 2003). In the case of lemborexant, the data from a radiolabeled ^{14}C-human mass balance study indicate that lemborexant is extensively metabolized since only less than 13% of administered dose was recovered unchanged in feces only. Urinary excretion of unchanged lemborexant was not detectable indicating renal clearance is negligible. The proposed metabolic pathways of lemborexant involve primarily oxidation of dimethylpyrimidine moiety of lemborexant to the M4, M9, and M10 metabolites. These metabolites accounted for 6.6%, 6.3%, and 12.5% of the total drug-related $AUC_{(0\text{-}96h)}$, respectively. In vitro studies

also identified these human in vivo metabolites and indicated CYP3A-mediated metabolism as the predominant clearance pathway for lemborexant. Overall, these results indicate that lemborexant meets regulatory standards requiring assessment of the impact of hepatic impairment on PK.

7.2 Study Rationale

This study is being conducted to assess whether mild or moderate hepatic impairment influences the PK and metabolism of lemborexant, with the findings of this study anticipated to guide future dosing recommendations in patients with various degrees of hepatic impairment. Based on data from drug interaction with itraconazole as well as CYP3A-mediated metabolism being the predominant clearance pathway for lemborexant, it is anticipated that a strong effect will be observed in severe hepatic impaired subjects, which will impact the PK of lemborexant, thus leading to contraindications in this subgroup of hepatic impairment subjects. To mitigate the anticipated effect of hepatic function on lemborexant disposition, ongoing Phase 3 studies do not include subjects with severe hepatic disease, however, they do allow for enrollment of subjects with mild and moderate impairment, which likely reflects the anticipated insomnia patient population Therefore, the proposed study limits the population to mild and moderate impaired subjects only. Furthermore, a population PK analysis applied to data from phase 2 and 3 studies will also be utilized to formulate a comprehensive dosing recommendation relevant to the mild and moderate hepatic-impaired subjects.

7.2.1 Study Design

The overall study design proposed, including the dose, regimen, number of healthy control subjects, endpoints, and analyses follows the recommendations from the latest guidelines by FDA and EMA on evaluation of PK in subjects with hepatic impairment (FDA, 2003; EMA, 2005).

The proposed study design includes the enrollment of patients with mild and moderate liver impairment (Child-Pugh class A and B respectively). Subjects with severe hepatic impairment (Child-Pugh class C) will be excluded from the study as outlined above.

The regulatory guidelines include a provision for use of a reduced, sequential study design, to evaluate the group of subjects with higher severity of liver impairment first (such as moderate liver impairment), and if no effect on PK is demonstrated, then these results could be extrapolated to the subjects with liver impairment of lesser severity. In the case of lemborexant, the reduced study design is considered to be unsuitable since a large effect in the moderate hepatic impaired subjects is expected based on the current disposition profile for lemborexant. This design would require subsequent investigation in mild hepatic impaired subjects to ensure clarity regarding lemborexant labeling.

The proposed study design includes 8 subjects per cohort of mild and moderate hepatic impairment and 8 matched control subjects, and will utilize an estimation-based approach to calculate the ratios of the geometric means rather than powering the study to test for a

specific difference in exposure between subjects with hepatic impairment and healthy controls. In addition, 90% CIs for the slope parameter of the relationship between Child-Pugh score and apparent clearance of lemborexant may provide additional indication of any effect (or lack of) on lemborexant PK. This analysis will take into account all subjects' data (N=24), thereby increasing the possibility to detect a relationship between severity of liver impairment and lemborexant PK.

7.2.2 Assessment of Severity of Liver Impairment

As proposed for the study, both guidelines (FDA, 2003; EMA, 2005) recommend use of Child-Pugh Classification Score as a marker of degree of liver impairment. The EU guidelines also recommend obtaining the adequate range of decreases in serum albumin and increases in bilirubin and prothrombin times. Unlike serum creatinine or creatinine clearance, which have been used to assess the degree of renal impairment, there is no single measure or group of measures that has gained widespread clinical use to estimate the degree of liver impairment. As the Child-Pugh classification system is based on laboratory-based parameters (serum albumin, bilirubin and prothrombin time) and also 2 clinical features (encephalopathy and ascites), the total score relies on the subjective assessments of these features, and hence is associated with variability in estimation of the degree of impairment. Among other models that have been increasingly used as a measure of liver impairment, the model of end stage liver disease (MELD) score, relies only on the laboratory parameters, and thus, is more likely to be consistent between different clinical centers for grading a particular patient for degree of liver impairment. In addition, published reports have indicated a good correlation between the MELD scores and Child-Pugh Scores (Albarmawi et al 2013). Therefore, as per the regulatory guidelines, although the proposed study will use the Child-Pugh Classification as a primary approach for characterizing degree of liver impairment, an exploratory assessment of the correlation between the lemborexant PK and the MELD score will be included to aid clinical guidance. Nonetheless, in agreement with the guidelines, the overall conclusions and dosing recommendations will be based on analysis using the Child-Pugh Scores and their relationship with lemborexant PK.

7.2.3 Choice of Dose, Regimen, and PK Assessments

A single-dose study design is proposed based on the following PK characteristics of lemborexant and is in agreement with regulatory guidelines. Following single-dose administration in healthy volunteers, lemborexant was safe and well tolerated up to 200 mg and demonstrated approximate dose-proportional PK up to 75 mg with no time-dependency in plasma exposures upon multiple dosing. The main metabolites, including M4, M9, and M10, are pharmacologically active in vitro but are also P-glycoprotein (P-gp) substrates; therefore the likelihood to penetrate into the central nervous system (CNS) would be low. The half-lives of the M4, M9, and M10 metabolites were similar to lemborexant accounting for 6.3%, 6.6%, and 12.5% of the total plasma exposure ($AUC_{0\text{-}96h}$. In addition, the AUC metabolite to parent ratios at steady state was approximately 19.9% to 57.5% for a 2.5-fold higher dose (ie, 25 mg) than the current planned dose level of 10 mg lemborexant. Taken together, these findings support the conclusion that using a single dose of lemborexant is appropriate and translatable to the effect at steady state.

The choice of the 10-mg dose is based on the fact that it is the highest dose being studied in the ongoing Phase 3 studies, and is also likely to be the selected dose for final registration. Taking into consideration the safety and tolerability of lemborexant in healthy volunteers from single ascending doses up to 200 mg, the predicted exposure and safety margins for lemborexant at 10 mg in the hepatic impaired subjects are well covered.

With lemborexant as the only pharmacologically active moiety, the primary PK endpoints for the study will be the total C_{max} and AUC parameters for lemborexant, whereas the PK comparisons for the metabolites will be secondary endpoints. In order to account for potential prolongation of the half-life of lemborexant or metabolites in subjects with liver impairment, the PK samples will be collected up to Day 14 after dosing. One of the key assessments stipulated in all regulatory guidelines for special population studies (ie, renal and hepatic impairment) is the evaluation of any change in the unbound fraction of the pharmacologically active moieties in vivo and assessment of the relationship between the unbound plasma exposures (AUC_u) and apparent clearance with measures of liver impairment, where binding of the drug to plasma proteins is high (eg, >90%). With lemborexant and its main metabolites (M4, M9, and M10), plasma protein binding based on in vitro studies is approximately 88%, 74%, 86%, and 92% bound to human plasma, respectively, and linear over the clinically observed concentrations. Due to the marginally high plasma protein binding of lemborexant and its metabolites in the current study, 2 blood samples will be collected, one at the maximum plasma exposure time and one at trough level. The respective unbound PK parameters for lemborexant will be derived by applying the unbound ratio to the PK parameters calculated using total plasma concentrations of lemborexant. Plasma protein binding of metabolites will be assessed to compare these results to in vitro data and assess any difference between hepatic impaired subjects and healthy volunteers that is currently not anticipated. The analysis of the unbound PK parameters (lemborexant only) between subjects with liver impairment and normal controls will be considered as secondary PK parameter endpoints only.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective is to assess the effect of mild and moderate hepatic impairment on the PK of lemborexant after a single dose administration.

8.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effects of hepatic impairment on the PK of lemborexant metabolites M4, M9, and M10.
- To evaluate the relationship between the PK parameters of lemborexant and its metabolites and the Child-Pugh Classification score, serum albumin, total bilirubin, and prothrombin time.

- To assess safety and tolerability of lemborexant following a single dose administration in subjects with mild and moderate hepatic impairment and healthy subjects.

8.3 Exploratory Objectives

The exploratory objectives are:

- To explore the relationship between the PK parameters of lemborexant and its metabolites and the model of end stage liver disease (MELD) score.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-A001-104 is a multicenter, single dose, open-label, parallel-group study in subjects with mild and moderate hepatic impairment and matched (with regard to age [±10 years], sex, and body mass index [BMI, ±20%]) healthy control subjects. The study will enroll a total of 24 subjects, including 16 subjects with impaired hepatic function; 8 subjects each in Child-Pugh class A (mild) and B (moderate). At least 8 healthy subjects will be dosed as one control cohort to match (1:1) to the subjects with hepatic impairment in each Child-Pugh class with regard to age, sex, and BMI.

The study will consist of 2 phases: Prerandomization and Treatment. The Prerandomization Phase will include 2 study periods; Screening and Baseline (Day -1). The subjects will be admitted to the clinical facility on Day -1, remain confined to the clinic until Day 8, and then return to the clinical facility for additional PK sampling as outpatients until Day 14. In the event of early discontinuation of the subjects, the subjects with Child Pugh Class A and B (Cohorts A and B) and the matched controls (Cohort C) may be replaced.

On Day 1, the subjects will be administered a single 10-mg dose of lemborexant with approximately 240 mL of water in the morning after an overnight fast. The blood samples for PK assessments will be collected at prespecified intervals up to 312 hours postdose administration. The subjects will be discharged on Day 14 of the study. In addition, the blood samples for plasma protein binding assessments of lemborexant will be collected from each subject at 2 time points; approximately 1 hour and 24 hours postdose.

The end of the study will be the date of the last study visit for the last subject.

9.1.1 Prerandomization Phase

The Prerandomization Phase will include a Screening Period and a Baseline Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. Screening period assessments and timing thereof are shown in Section 9.5.2.

9.1.1.2 Baseline Period

The purpose of the Baseline Period is to confirm protocol eligibility and to obtain baseline data for assessment. Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Section 9.3.1 and Section 9.3.2) will begin the Treatment Phase. Baseline assessments and timing thereof are shown in Section 9.5.2.

9.1.2 Treatment Phase

The Treatment Phase will consist of 1 study period of 14 days. The Treatment Phase assessments and timing thereof are shown in Section 9.5.2.

9.2 Discussion of Study Design, Including Choice of Control Groups

This single dose, parallel-group study aims to investigate the effects of mild and moderate hepatic impairment on the PK of lemborexant and its main metabolites (M4, M9, and M10). At least 24 subjects will be enrolled, and 16 of these subjects will have impaired (mild or moderate) hepatic function. The other approximately 8 subjects will be healthy and will serve as the control group. Healthy subjects will be matched (1:1) with the 8 subjects with mild hepatic impairment and the 8 subjects with moderate hepatic impairment according to age (±10 years), sex, and BMI (±20%).

The data from this study will help guide specific dosing recommendations in insomnia disorder and/or ISWRD patients with impaired hepatic function and establish labeling recommendations for this new chemical entity.

Adjudication Committee (revised per Amendment 01)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [standardized MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia, [faintness] and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the serious adverse event (SAE) form for any of the above events considered serious.

9.3 Selection of Study Population

A total of 24 subjects will be enrolled in each of the following 3 cohorts:

Cohort A: 8 subjects with mild hepatic impairment (Child Pugh Class A)

Cohort B: 8 subjects with moderate hepatic impairment (Child Pugh Class B)

Cohort C: At least 8 healthy subjects (control) matched to subjects in Cohorts A and B

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Inclusion Criteria for All Subjects

Subjects who meet all of the following inclusion criteria will be eligible for participation in the study.

1. Male or female subjects, ages 18 to 79, inclusive, at the time of informed consent.
2. BMI between 18 and 40 kg/m^2, inclusive, at Screening.
3. Voluntary agreement to provide written informed consent, and the willingness and ability to comply with all aspects of the protocol.
4. Nonsmokers or smokers who smoke 20 cigarettes or less per day.
5. For Cohorts A and B: stable (without any change in disease status for at least 60 days prior to study screening) hepatic impairment conforming to Child-Pugh classification A or B, respectively (see Table 1 and Table 2), and documented by medical history and a physical examination.
6. For Cohort C: healthy subjects matched to subjects with hepatic impairment 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, electrocardiogram (ECG), and clinical laboratory determinations.

Table 1 Criteria for Child-Pugh Classification			
	Points Scored for Observed Findings		
Clinical or Biochemical Assessments	**1**	**2**	**3**
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
Bilirubin (mg/dL)	<2	2 – 3	>3
PT (seconds prolonged)	<4	4 – 6	>6
or INR	<1.7	1.7 – 2.3	>2.3
Ascites	None	Mild/Moderate (diuretic-responsive)	Tense (diuretic-refractory)
Encephalopathy[a]	None	1 or 2 (or precipitant-induced)	3 or 4 (chronic)

cps=cycle per second; INR=international normalized ratio; PT=prothrombin time

a: Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram; Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, and 5 cps waves; Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves; Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves; Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Table 2 Child-Pugh Classification Scoring	
Total Points	**Child-Pugh Class**
5 – 6	A
7 – 9	B

9.3.2 Exclusion Criteria

Exclusion Criteria for All Subjects

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the dose of study drug.

2. Females of childbearing potential who did not use a highly effective method of contraception (as described below) within 28 days before study entry, or who do not agree to use an approved method of contraception from 28 days before study entry, throughout the entire study period, and for 28 days after study drug discontinuation. Approved (highly effective) methods of contraception for this study include at least one of the following:
   - Total abstinence (if it is their preferred and usual lifestyle)
   - An intrauterine device or intrauterine hormone-releasing system (IUS)
   - A double-barrier method of contraception such as condom plus diaphragm with spermicide
   - A contraceptive implant

- An oral contraceptive (with additional barrier method). Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.
- Have a vasectomized partner with confirmed azoospermia.

(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

3. Known to be positive for human immunodeficiency virus (HIV).

4. Currently enrolled in another clinical study or used any investigational drug or device within 4 weeks, or 5 times the half-life of the investigational drug (whichever is longer), preceding informed consent.

5. Receipt of blood products within 4 weeks, or donation of blood within 8 weeks, or donation of plasma within 1 week of dosing until study discharge.

6. Intake of herbal preparations containing St. John's Wort within 4 weeks prior to dosing until study discharge.

7. Intake of nutritional supplements (including herbal preparations), foods or beverages that may affect CYP3A enzyme (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 1 week before dosing until study discharge.

8. Intake of beverages, food, or other products that contain caffeine from 24 hours before until 48 hours after dosing with lemborexant.

9. Engagement in strenuous exercise (eg, moving large bulky items, bodybuilding) within 2 weeks prior to check-in until study discharge.

10. History of clinically significant drug or food allergies, or is presently experiencing significant seasonal allergies.

11. A prolonged QT/QTc interval (QTc >480 ms) demonstrated on ECG at Screening or Baseline (Day -1).

12. Any major surgery within 4 weeks of study drug administration.

13. Any history of abdominal surgery that may affect PK of lemborexant (eg, hepatectomy, nephrectomy, digestive organ resection).

14. Inability to tolerate oral medication.

15. Inability to tolerate venous access and/or venipuncture.

16. Unwilling to abide by the study requirements, or in the opinion of the investigator, is not likely to complete the study.

Additional Exclusion Criteria for Hepatically Impaired Subjects (Cohorts A and B)

In addition to the Exclusion Criteria above for All Subjects, other standard exclusion criteria for subjects with hepatic impairment will be used. These include:

17. Any significant acute medical illness (such as new conditions or exacerbation of pre-existing conditions) within 8 weeks of dosing.

18. Medical conditions which are not adequately and stably controlled on stable doses of medications or which, in the clinical opinion of the Principal Investigator, may interfere with study procedures or subject safety within 4 weeks before dosing (eg, psychiatric disorders and disorders of the gastrointestinal tract, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or subjects who have a congenital abnormality in metabolism).

19. History of esophageal and gastric variceal bleeding within the past 6 months unless the subject has completed a course of endoscopic therapy with the appropriate documentation (eg, endoscopy report) of successful ablation of esophageal varices; subjects with esophageal varices may be included if not bleeding within the past 6 months or have been treated adequately by ablation therapy, as specified above.

20. Spontaneous bacterial peritonitis within 3 months of dosing.

21. Treatment with plasmapheresis within 6 months of dosing.

22. Primarily cholestatic liver diseases (eg, primary biliary cirrhosis or primary sclerosing cholangitis).

23. Current or recent (within 3 months prior to screening) history of significant gastrointestinal disease other than that secondary to hepatic impairment.

24. Autoimmune liver disease.

25. Active alcoholic hepatitis determined either clinically or by histology.

26. History of hepatoma or metastatic disease of the liver.

27. Presence of severe ascites or edema.

28. Presence of hepatopulmonary syndrome or hydrothorax, or hepatorenal syndrome.

29. Known significant bleeding diathesis that could preclude multiple venipunctures (INR >2.5).

30. Creatinine clearance <60 mL/min at Screening or Baseline as calculated using Cockroft and Gault Equation.

31. The subject's standard therapy/concomitant medication for diseases related to cirrhosis has not remained stable/unchanged for at least 14 days before the first dose of study drug.

32. History of drug or alcohol dependency or abuse within 4 weeks prior to Screening, or those who have a positive urine drug test or breath alcohol test at Screening or Baseline unless a prescribed medication for the underlying condition is the cause of the positive urine screen.

Additional Exclusion Criteria for Healthy Subjects (Cohort C)

In addition to the Exclusion Criteria for All Subjects, other standard exclusion criteria for healthy subjects in Phase 1 studies will be used. These include:

33. Presence of active liver disease, or acute liver injury, as indicated by (1) an abnormal liver function test, or (2) clinical or laboratory signs of active viral hepatitis (including B and C, as demonstrated by positive serology at Screening).
34. Clinically significant illness, within 4 weeks prior to dosing, that requires medical treatment or may influence the outcome of the study; eg, psychiatric disorders and disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or subjects who have a congenital abnormality in metabolism.

35. Any abnormal finding based on physical examination, assessment of vital signs, ECG, or laboratory test results that require treatment or clinical follow-up based on the investigator's opinion.

36. History of drug or alcohol use disorder within the 2 years prior to Screening, or those who have a positive urine drug test or breathalyzer alcohol test at Screening or Baseline.

37. Use of any prescription drugs within 4 weeks prior to dosing until study discharge.

38. Intake of any over-the-counter (OTC) medications within 2 weeks prior to dosing until study discharge.

9.4 Treatments

Test drug: lemborexant (E2006)

Comparator Drug: Not applicable

9.4.1 Treatments Administered

All subjects enrolled in the study will receive a single 10-mg dose (1 × 10 mg lemborexant tablet) in the morning after an overnight fast.

9.4.2 Identity of Investigational Product

Test drug will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name, Structural Formula of E2006

- Test drug code: E2006
- Generic name: Lemborexant tablet
- Chemical name: (1R,2S)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide
- Molecular formula: $C_{22}H_{20}F_2N_4O_2$
- Molecular weight (molar mass): 410.42 g/mol

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Lemborexant will be labeled in English with text that is in full compliance with US regulations.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to 1 of 3 cohorts: subjects with mild hepatic impairment (Child Pugh Class A) will be in Cohort A, subjects with moderate hepatic impairment (Child Pugh Class B) will be in Cohort B, and healthy (control) subjects will be in Cohort C. To qualify for Cohort A or B, the subject must have stable (ie, without any change in disease status for at least 60 days prior to study screening) hepatic impairment conforming to Child-Pugh

classification A or B, respectively (see Table 1 and Table 2), documented by medical history and a physical examination. To qualify for Cohort C, the healthy subject must match a subject with hepatic impairment 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.

9.4.4 Selection of Doses in the Study

Lemborexant 10 mg proposed in this study is consistent with the highest dose being tested in Phase 3 clinical trials for insomnia disorder.

9.4.5 Selection and Timing of Dose for Each Subject

Following an overnight fast of at least 10 hours, subjects will be administered the study drug product in the morning with 240 mL (8 fluid ounces) of water. No food will be allowed for at least 4 hours postdose. Water will be allowed as desired except for 1 hour before and after drug administration.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter [OTC] medications) or therapy administered to the subject within 30 days prior to Screening until the end of study participation will be recorded on the Prior and Concomitant Medication case report form (CRF) or Non−Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered.

The following prior and concomitant therapies are prohibited for all subjects:

- Nutritional supplements, juice, and herbal preparations or other foods or beverages that may affect the various drug metabolizing enzymes and transporters (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], and charbroiled meats) within 1 week before dosing until study discharge.
- Herbal preparations containing St. John's Wort within 4 weeks before dosing until study discharge.

The following prior and concomitant therapies are prohibited for healthy subjects:

- Use of prescription drugs is prohibited from at least 4 weeks before dosing until study discharge.

- Use of over-the-counter (OTC) medications is prohibited from at least 2 weeks before dosing until study discharge.

Subjects with hepatic impairment may receive standard therapy approved by the Medical Monitor for diseases related to cirrhosis; however, the following restrictions apply:

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

See Appendix 2 for a full list of prohibited concomitant medications.

9.4.8 Prohibitions and Restrictions during Study Period

9.4.8.1 Food and Water

Menus will be standardized while subjects are inpatients in the study unit. The menus will be the same for all subjects; however, the menus for each inpatient day need not be identical. Subjects must consume only the food given to them while in the unit. Food and water will be restricted as follows:

Day -1 (Baseline)

- Subjects will be given an evening snack following check-in to the study unit on the day before dosing. They will fast (only water is permitted) for at least 10 hours prior to dosing.

Day 1 (day of dose administration)

- Subjects will fast (only water is permitted) for at least 4 hours after dosing. Fluid will be restricted (240 mL water at time of oral dosing) from 1 hour before dosing until 1 hour after dosing.
- A low-fat lunch (<30% fat), an afternoon snack, dinner, and an evening snack will be provided at appropriately scheduled times.

Days 2 through 7

- A similar schedule and menu for meals/snacks will be followed on each day after dosing until clinic discharge. There will be free access to drinking water throughout each day.

9.4.8.2 Beverage and Other Restrictions

- Intake of beverages, food, or other products that contain caffeine from at least 24 hours before until at least 48 hours after dosing with lemborexant.

- Intake of nutritional supplements, juice, herbal preparations, or other foods or beverages that may affect CYP3A enzyme or transporters (eg, alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [eg, kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard] and charbroiled meats) within 1 week before dosing until study discharge.

- Smokers must not smoke more than 20 cigarettes per day.

9.4.8.3 Physical Activity Restrictions

- Engagement in strenuous exercise is prohibited within 2 weeks before check-in on Day -1 and until study discharge.

- Subjects should maintain an upright (greater than 45° angle) position for at least 4 hours following administration of study drug, except for AEs or study-related procedures requiring a different position.

9.4.9 Treatment Compliance

All doses will be administered by qualified research site personnel ensuring compliance to the protocol-specified dosing regimens. Each subject's dose will be administered at the designated dosing time and documented in the source documents maintained on site. At the end of each tablet dose, a hand and mouth check will be performed to ensure that the entire dose of study drug has been properly consumed.

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s).

Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race/ethnicity, and BMI.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All clinically significant medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 HEIGHT AND WEIGHT MEASUREMENTS

Height (cm) and weight (kg) will be recorded and BMI will be determined at the Screening Visit. Subjects will have their weight (kg) measured again on Day -1.

9.5.1.3 Efficacy Assessments

Not applicable.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Plasma concentration of Lemborexant

Blood samples (4 mL each) will be collected as specified in the Schedule of Procedures/Assessments (Table 4). A separate lab manual will be provided for a description of collection, handling, and shipping procedures of the plasma samples for PK analysis. In

addition, blood samples for protein binding (12 mL per time point) of lemborexant will be collected at 1 and 24 hours postdose matching the PK sample collection at those time points.

Total plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) will be measured by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. The unbound concentrations of lemborexant, M4, M9, and M10 will also be measured using a similar validated LC-MS/MS method following equilibrium dialysis.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in Table 4.

9.5.1.5.1 **ADVERSE EVENTS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lemborexant.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Note: Every sign or symptom should not be listed as a separate AE if the applicable disease (diagnosis) is being reported as an AE
- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase and for 28 days after the subject's last dose. Serious AEs will also be collected for 28 days after the last dose (or 5 times the half-life, whichever is longer).

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

All AEs must be followed for 28 days (or 5× the half-life, whichever is longer) after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for PK analysis should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection and are to be fasting for at least 4 hours before blood is drawn for clinical laboratory measurements. The Schedule of Procedures/Assessments (Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell (RBC) count, and white blood cell (WBC) count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Coagulation Panel	Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
Chemistry	
Electrolytes	Chloride, potassium, sodium, calcium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Other	Total protein, globulin, albumin, cholesterol, triglycerides, glucose, lactate dehydrogenase, uric acid, and creatinine (revised per Amendment 01)
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs
Virology	Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb)

Clinical laboratory tests during the study will be performed by a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 4) by a validated method. Blood pressure and pulse will be measured after the subject has been in supine position for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Comprehensive and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. The subject will be queried regarding physical status and subjective symptoms as well.

Abbreviated/Routine Physical Examination

Health status will be assessed by brief evaluation of the chest (including heart and lungs), abdomen and limbs, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.5.6 ELECTROCARDIOGRAMS

Twelve-lead electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 4).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.5.7 VIRAL TESTS

An 8.5 mL sample of blood will be taken for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) at Screening.

9.5.1.5.8 PREGNANCY TEST

At Screening, a serum pregnancy (β-hCG test) will be performed for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months using the 8.5 mL blood sample taken for clinical laboratory tests. These women will have a urine pregnancy test after Screening at the designated time points specified in the Schedule of Procedures/Assessments (Table 4).

9.5.1.5.9 URINE DRUG TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 4). This sample will be tested for common drugs of use/abuse: eg, cocaine, cannabinoids, PCP, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.1.5.10 BREATH ALCOHOL TEST

The breath alcohol test will be performed according to the investigational site's SOP at designated time points as specified in the Schedule of Procedures/Assessments (Table 4).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the study.

Table 4 Schedule of Procedures/Assessments in E2006-A001-104

Study Phase	Prerandomization		Treatment						
Period	**Screening**	**Baseline**							
Visit	**1**	**2**					**3**	**4**	**5/Early Discontinuation**
Day(s)	**-21 to -2**	**-1**	**1**	**2**	**3, 4, 5, 6, 7**	**8**	**10**	**12**	**Day 14/ET**
Assessment									
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Medical History and Demographics	X								
Comprehensive Physical Exam	X								
Abbreviated/Routine Physical Exam		X				X			X
Height, Weight, and BMI	X	X [a]:							
Vital Signs [b]:	X	X	X	X		X	X	X	X
12-lead ECG [c]:	X	X	X	X					X
Viral Screen (hepatitis B and C)	X								
Urine Drug Test	X	X							
Alcohol Breathalyzer	X	X							
Serum β-hCG Pregnancy Test [d]:	X								
Urine Pregnancy Test [d]:		X							X
Clinical Lab Tests (Hematology, Clinical Chemistry, and Urinalysis) [e]:	X	X		X					X
PT, aPTT, and INR	X	X		X					X
PK Blood Sample [f]:			X	X	X	X	X	X	X
Blood Sample for Protein Binding Assessment [g]:			X	X					
Administer Lemborexant [h]:			X						
Admission to Clinic		X							
Release from Clinic [i]:						X			
Discharge from Study [j]:									X
Adverse Events	←----------								----------→
Prior/Concomitant Medications	←----------								----------→

aPTT=activated partial thromboplastin time; β-hCG= beta-human chorionic gonadotropin; BMI=body mass index; ECG = electrocardiogram; ET= early

termination; INR= international normalized ratio; PK=pharmacokinetic; PT=prothrombin time

a: Only weight will be recorded at Baseline (Day -1).

b: Single measurements of vital signs (blood pressure, heart rate, body temperature, and respiratory rate) after at least 5 minutes of supine rest will be recorded at Screening, clinic check-in on Day -1, predose on Day 1, Day 2, prior to clinic discharge on Day 8, on Days 10 and 12, and at end-of study (Day 14 or early termination).

c: Single ECG will be recorded at Screening, Baseline (Day -1), Day 1 (predose and 3 hours postdose), Day 2 (24 hours postdose), and Day 14 (312 hours postdose). A variance of ±15 minutes is allowed. Before excluding a subject with QTcF > 480 at Screening, ECG should be repeated once to confirm.

d: Females of childbearing potential only.

e: Subjects will fast for at least 4 hours before blood is drawn for clinical laboratory assessments. Measurement of serum albumin and creatinine will be part of the central laboratory tests. (revised per Amendment 01)

f: Blood samples (4 mL per time point) for PK assessments will be collected on Day 1 (predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose), Days 2 (24 hours postdose), 3 (48 hours postdose), 4 (72 hours postdose), 5 (96 hours postdose), 6 (120 hours postdose), 7 (144 hours postdose), 8 (168 hours postdose), 10 (216 hours postdose), 12 (264 hours postdose) and 14 (312 hours postdose). If a subject is early terminated, he or she will not have a blood sample collected for PK unless early termination coincides with a scheduled PK time point. A variance of ±5 minutes (up to the first 2 hours postdose), ±10 minutes for time points up to, and including, Day 8 (168 hours postdose) and ±2 hours for Day 10 (216 hours postdose) to Day 14 (312 hours postdose) is allowed.

g: Blood samples (12 mL per time point) for plasma protein binding will be collected at approximately 1 and 24 hours postdose, matching with the time collection for PK samples for lemborexant and its main metabolite, M4, M9 and M10.

h: A single 10-mg dose of lemborexant as 1 × 10 mg tablet will be administered with 240 mL of water following an overnight fast. Dosing will be in the morning followed by a 4-hour postdose fast. Water will be allowed ad libitum except for the interval from 1 hour before to 1 hour after study drug administration.

i: Subjects will be released from the clinic after completing the Day 8 procedures and then return to the clinic for outpatient visits on Days 10, 12, and 14.

j: Subject will be released from the study after completion of Day 14 (end-of-study) procedures or early termination.

Table 5 presents the blood sampling schedule for PK assessments.

Table 5 Blood Sampling Schedule for Pharmacokinetic Assessments

Study day	Time (on each day)	Acceptable time-window
Day 1	Predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose	Predose; -1 hour Postdose (up to first 2 hours postdose); ±5 minutes Postdose (after 2 hours postdose); ±10 minutes
Day 2	24 hours postdose	±10 minutes
Day 3	48 hours postdose	
Day 4	72 hours postdose	
Day 5	96 hours postdose	
Day 6	120 hours postdose	
Day 7	144 hours postdose	
Day 8	168 hours postdose	
Day 10	216 hours postdose	±2 hours
Day 12	264 hours postdose	
Day 14	312 hours postdose	

9.5.2.2 Total Volume of Blood Sampling

Table 6 presents the number of blood samples and the total volume of blood that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure subject safety.

Table 6 Summary of Blood Sample Volumes

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	8.5	Screening (including pregnancy testing): 1 Baseline (Day -1): 1 Day 2: 1 Day 14 or early termination: 1	8.5×4=34
Viral test	8.5	Screening: 1	8.5×1=8.5
PK blood sampling	4	20	4×20=80
Blood sampling for plasma protein binding	12	2	2×12=24
Total			**146.5**

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in bioavailability studies.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event (revised per Amendment 01).

SAEs, regardless of causality assessment, must be collected through the last visit in the Treatment Phase and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues call: PPD **(24/7 number).**

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. (revised per Amendment 01) If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Association with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigator and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable

9.5.4.6 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 4).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may be replaced.

9.5.6 Confirmation of Medical Care by Another Physician (for Hepatic Impairment Subjects):

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed after the study is completed and the database is locked and released. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

The endpoints include the following PK parameters derived by non-compartmental analysis using the plasma concentration-time data of lemborexant and its metabolites:

C_{max}	Maximum plasma concentration
t_{max}	Time to reach maximum plasma concentration
$AUC_{(0-t)}$	Area under plasma concentration vs. time curve from time = 0 to time of last quantifiable concentration
$AUC_{(0-inf)}$	Area under plasma concentration vs. time curve from time = 0 to infinity
$t_{1/2}$	Terminal phase plasma half-life
CL/F	Apparent total body clearance (for lemborexant only)
Vz/F	Apparent volume of distribution (for lemborexant only)
AUC Metabolite Ratio	Ratio of $AUC_{(0-inf)}$ of individual metabolite to $AUC_{(0-inf)}$ of lemborexant, corrected for molecular weights
fu	Plasma protein unbound fraction
AUCu	$AUC_{(0-inf)}$ values adjusted by unbound fraction in plasma (for lemborexant only)
CLu/F	Apparent clearance relative to the unbound plasma concentration based on AUCu (for lemborexant only)

The C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ based on total exposures of lemborexant will be the primary PK endpoints. The rest of the parameters, including the PK parameters of the metabolites, will be secondary endpoints.

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who dosed with the test drug and had at least 1 postdose safety assessment.

The Pharmacokinetic Analysis Set is the group of subjects who dosed with the test drug and had sufficient PK data to derive at least 1 PK parameter.

9.7.1.3 Subject Disposition

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the safety analysis set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, weight, height, BMI, and for subjects with hepatic impairment: MELD score and Child-Pugh classification; categorical variables include sex, ethnicity, and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD, March 2017). Prior medications will be defined as medications that stopped before the dose of study drug. Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication CRF or Non-Pharmacological Procedures CRF. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Not applicable.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for individual plasma concentration listings. The PK Analysis Set will be used for summaries of plasma concentrations and for analyses, summaries, and listings of PK parameters.

The effect of hepatic impairment on the PK of lemborexant, the primary PK parameters based on total C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ will be compared between the cohort of healthy normal controls and the cohorts of subjects with mild and moderate hepatic impairment as defined by Child-Pugh classes A or B. A general linear model of logarithmically transformed values with hepatic function class as a fixed effect will be utilized to estimate the geometric mean ratio (and two-sided 90% confidence intervals) of subjects with mild/normal and moderate/normal hepatic function. Similar statistical analyses will be conducted for the PK parameters of the metabolites and unbound lemborexant as secondary endpoints. Protein binding will be calculated for metabolites without any assessment of PK parameters.

Scatter plots of PK parameters of lemborexant and its metabolites versus Child-Pugh Score will be provided. The association between the primary PK parameters and Child-Pugh Score will be evaluated by regression analysis (the PK parameter as a dependent variable and Child-Pugh Score as an independent variable). Similar analyses will be performed for

MELD score, serum albumin, total bilirubin, and PT. Additionally, association between the PK parameters and liver transaminase levels will be performed, if deemed necessary.

Summary statistics will be generated for each of the PK parameters for each Child-Pugh class and healthy controls.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

An evaluation of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and ECGs.

Treatment-emergent adverse events (TEAEs) will be summarized for each Child-Pugh class and healthy controls. Descriptive summary statistics (eg, mean, standard deviation [SD], median, minimum, maximum for continuous variables, and number and percent for categorical variables) including shift tables of the laboratory, vital signs, ECG parameters. Changes from Baseline for the clinical laboratory, vital signs and ECG parameters will be evaluated for each Child-Pugh class and healthy controls by time point.

9.7.1.8.1 EXTENT OF EXPOSURE

All subjects enrolled in the study will receive a single 10-mg dose (1 × 10 mg lemborexant tablet) in the morning after an overnight fast.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 20.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted

only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

Subject data listings of AEs, TEAEs leading to death, SAEs, and AEs leading to withdrawal will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-group comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment.

Clinical laboratory results post baseline will be evaluated for markedly abnormal values.

Appendix 1 presents the Sponsor's grading for laboratory values that will be used to identify subjects with markedly abnormal laboratory values.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by day and time after dosing and group.

9.7.1.8.5 ELECTROCARDIOGRAMS

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

9.7.2 Determination of Sample Size

A sample size of 8 subjects per each cohort of mild and moderate hepatic impairment, as defined by Child-Pugh classes A or B, is based on the recommendations in regulatory guidelines for a minimum number of subjects to be enrolled for moderate liver impairment

cohort (FDA, 2003). Additionally, from single-dose studies of the 10-mg tablet (E2006-A001-004, E2006-A001-005, and E2006-A001-008), the pooled between-subject standard deviations of logarithmically transformed C_{max} and $AUC_{(0\text{-inf})}$ of lemborexant were 0.334 and 0.391 respectively. With a sample size of 8 subjects in each Child-Pugh category and at least 8 matched controls, a 2-sided 90% confidence interval (CI) for the ratio for $AUC_{(0\text{-inf})}$ will extend 0.322 from the observed mean difference on the log scale.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. Albarmawi A, Czock D, Gauss A, Ehehalt R, Bermejo JL, Burhenne J, Ganten T, Sauer P, and Haefeli W. CYP3A activity in severe liver cirrhosis correlates with Child-Pugh and model for end-stage liver disease (MELD) scores. Br J Clin Pharmacol, 2013;77(1),160-169.

2. Heizmann P, Eckert M, Ziegler WH. Pharmacokinetics and bioavailability of midazolam in man. Br J Clin Pharmacol. 1983;16 (Suppl 1):43S‑49S.

3. Lai AA and Schroeder DH. Clinical pharmacokinetics of bupropion: a review. J Clin Psychiatry.1983;44(5 Pt 2):82‑4.

4. Food and Drug Administration Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function- Study Design, Data Analysis, and Impact on Dosing and Labeling [updated May 2003; cited 12 Dec 2017]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf.
5. European Medicines Agency. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function. 17 Feb 2005. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf.
   Accessed on 28 Dec 2017.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.1 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.2 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images,

ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives

- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.3 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.4 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.5 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.6 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.7 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor or designee. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designee, when approval is given by the sponsor, the investigator (or a designated pharmacist) will destroy supplies and containers at the site.

11.8 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.9 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.10 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.11 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 List of Prohibited Concomitant Medications

If a medication is not presented in the list below, but does fit into a class of medications noted in the list, the medical monitor must be consulted to determine whether it is permitted.

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	Barbiturates Benzodiazepines GABA analogues Hydantoins Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter)	Diphenhydramine HCl Carbinoxamine Doxylamine Dimenhyrinate Triprolidine Bromopheniramine Chlorphemamine Hydroxazine
Antihistamines with known sedating effects	*Non-sedating, eg, loratadine is not prohibited*
Anxiolytics with known sedating effects	Lorazepam Alprazolam Buspirone
Strong CYP3A inhibitors	Amiodarone Boceprevir Clarithomycin Cobicistat Conivaptan Danoprevir Eltegravir Fluvoxamine Idelalisib Indinavir Itraconazole Ketoconazole Lopinavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir

Category	Medication
Moderate CYP3A inhibitors	Amprenavir Aprepitant Atazanavir Casopitant Cimetidine Ciprofloxacin Crizotinib Cyclosporine Darunavir Diltiazem Dronedarone Erythromycin Faldaprevir Fluconazole Imatinib Netupitant Verampamil
CYP3A inducers	Avasimibe Carbamazepine Enzalutamide Phenobarbital Phenytoin Rifabutin Rifampin St John's Wort Extract Bosentan Efavirenz Etravirine Lersivirine Modafinil Nafcillin Talviraline Thioridazine
Hypnotics	Melatonin Prescribed or OTC
Herbal preparations with sedating effects	-
MAOIs	-
Opioid Analgesics	-
Muscle relaxants (centrally-acting) with known sedating effects	GABA analogues Hydantoins Phenyltriazines

Category	Medication
Stimulants	Amphetamines Modafinil Armodafinil Methylphenidate
Other	Warfarin, heparin, ticlopidine Non-stimulant diet pills Systemic isoretinoin Systemic glucocorticoids Tryptophan

PROTOCOL SPONSOR SIGNATURE PAGE

Study Protocol Number: E2006-A001-104

Study Protocol Title: An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant (E2006) and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects

Investigational Product Name: E2006/Lemborexant

IND Number: 111871

SIGNATURES

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-104
Study Protocol Title:	An Open-label, Parallel-Group Study to Evaluate the Pharmacokinetics of Lemborexant (E2006) and its Metabolites in Subjects with Mild and Moderate Hepatic Impairment Compared to Healthy Subjects
Investigational Product Name:	E2006/Lemborexant
IND Number:	111871

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date