

Revision History

Previous Version: v1.0

Current Version: v2.0

Date of Latest Revision: 12 Mar 2018 (revised per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Updated text in synopsis to align with text in the body of the protocol	Correction	Synopsis: <ul style="list-style-type: none">• Sites• Primary Objective• Study Design• Exclusion Criteria
Corrected typo	Correction	Section 8.1.2
Revised word for specificity	Correction	Section 8.2.1 Section 9.1.1.2.1

1 TITLE PAGE



CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2006-A001-102
Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Healthy Subjects and Adult and Elderly Subjects with Mild Obstructive Sleep Apnea
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 11 Dec 2017 (original protocol) V2.0 12 Mar 2018 (revised per Amendment 01)
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
Name of Active Ingredient: Lemborexant
Study Protocol Title A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Healthy Subjects and Adult and Elderly Subjects with Mild Obstructive Sleep Apnea
Investigator(s) TBD
Sites Approximately 10 investigational sites in the US (revised per Amendment 01)
Study Period and Phase of Development Phase 1 First Subject Screened to Last Subject Out: Approximately 5 months
Objectives Primary Objective (Healthy Volunteer [HV] Cohort) To determine whether lemborexant decreases the peripheral oxygen saturation (SpO ₂) during total sleep time (TST) in healthy adult and elderly subjects after a single dose of treatment compared with placebo Primary Objective (Obstructive Sleep Apnea [OSA] Cohort) (revised per Amendment 01) To determine whether lemborexant increases the AHI after multiple doses of treatment in adult and elderly subjects with mild OSA compared with placebo Secondary Objectives (HV Cohort) <ol style="list-style-type: none">1. Determine whether lemborexant increases the apnea-hypopnea index (AHI) after a single dose of treatment compared with placebo2. Determine whether lemborexant decreases SpO₂ during TST below defined thresholds after a single dose of treatment compared with placebo3. Evaluate safety and tolerability of lemborexant Secondary Objectives (OSA Cohort) <ol style="list-style-type: none">1. Determine whether lemborexant increases the AHI after the first dose of treatment compared with placebo2. Determine whether lemborexant decreases the mean SpO₂ during TST after the first and after multiple doses of treatment compared with placebo (revised per Amendment 01)3. Determine whether lemborexant decreases SpO₂ during TST below defined thresholds after the first and after multiple doses of treatment compared with placebo (revised per Amendment 01)4. Evaluate safety and tolerability of lemborexant

Exploratory Objectives (HV and OSA Cohorts)

Explore the effects of lemborexant compared with placebo after a single dose in HV Cohort and after the first and multiple doses in the OSA Cohort on the following:

1. The mean SpO₂ during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
2. AHI during REM and NREM sleep
3. AHI separately for adult and elderly subjects
4. The mean SpO₂ during TST separately for adult and elderly subjects

In addition, explore the following for both HV and OSA Cohorts:

1. Plasma concentrations of lemborexant and metabolites M4, M9, and M10
2. Exposure-response (E-R) relationships between lemborexant concentrations and pharmacodynamic (PD) variables, including but not limited to respiratory safety variables (AHI, mean SpO₂ during TST, proportion of TST during which the SpO₂ is decreased below defined thresholds)

Study Design (revised per Amendment 01)

E2006-A001-102 is a multicenter, multiple dose, randomized, double-blind, placebo-controlled, crossover study in adult and elderly healthy subjects and in adult and elderly subjects with mild obstructive sleep apnea (OSA).

Study 102 will consist of 2 cohorts: healthy subjects and subjects with mild OSA. The design of the study is based on the studies conducted with suvorexant in healthy volunteers and subjects with OSA.

HV Cohort

The HV Cohort comprises a randomized, double-blind, placebo-controlled, 3-period crossover study. Eligible healthy adult and elderly subjects will be randomized to treatment sequence A, B or C, each consisting of 3 Treatment Periods, each of one night’s duration, in which subjects will receive a single dose of lemborexant 10 mg, or lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 8 evaluable adult subjects (<65 years) and 4 evaluable elderly subjects (≥65 years) complete the study.

Treatment Sequence	Treatment Periods in the HV Cohort		
	1 (one night)	2 (one night)	3 (one night)
A	lemborexant-matched placebo	lemborexant 10 mg	lemborexant 25 mg
B	lemborexant 10 mg	lemborexant 25 mg	lemborexant-matched placebo
C	lemborexant 25 mg	lemborexant-matched placebo	lemborexant 10 mg

OSA Cohort

The OSA Cohort comprises a randomized, double-blind, placebo-controlled, 2-period crossover

study.

Adult and elderly subjects with mild OSA will be randomized to treatment sequences D or E, each consisting of 2 Treatment Periods, each of 8 nights' duration, in which subjects will receive lemborexant 10 mg or placebo. The Treatment Periods will be separated by a washout interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 20 evaluable adult subjects (<65 years) and 10 evaluable elderly subjects (≥65 years) complete the study.

Treatment Sequence	Treatment Periods in the OSA Cohort	
	1 (eight nights)	2 (eight nights)
D	lemborexant-matched placebo	lemborexant 10 mg
E	lemborexant 10 mg	lemborexant-matched placebo

Phases of the Study (HV and OSA Cohorts)

For both the HV and OSA cohorts, there will be 2 phases, Prerandomization and Randomization. The Prerandomization Phase for both cohorts will consist of the Screening Period (up to 21 days) and a Baseline Period (≤1day prior to randomization).

For the HV Cohort, the Randomization Phase will comprise 3 Treatment Periods, each of 1-day duration, separated by a washout interval of at least 14 days, followed by a 14-day Follow-Up Period.

For the OSA Cohort, the Randomization Phase will comprise 2 Treatment Periods, each of 8 days duration, separated by a washout interval of at least 14 days, and a Follow-Up Period of 14 days.

For both cohorts, an End of Study (EOS) Visit will occur at least 14 days after the final dose of study medication.

Prerandomization Phase - HV and OSA Cohorts

Screening Period

At the Screening Period, informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. All subjects will undergo routine safety assessments, including 12-lead electrocardiograms (ECG), physical examination, vital signs, weight, height, hematology, blood clinical chemistry analysis, urinalysis, viral serology, reporting of adverse events (AEs), and assessment of suicidality. (revised per Amendment 01)

A medical, psychiatric, and sleep history interview will be conducted; medical history will include history of falls. Female subjects of childbearing potential will undergo a serum pregnancy test. Subjects will be instructed on study restrictions pertaining to prohibited medications, drugs, alcohol, and caffeine. A urine drug test and breath alcohol test will be administered.

After at least 6 days (to allow subjects the opportunity to complete the sleep diary for at least 5 consecutive nights), subjects will return to the clinic for the second Screening Visit (Visit 2) to undergo polysomnography (PSG). On this and all other nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, scheduled assessments (including a urine drug test and breath alcohol test), as described in the Schedule of Assessments/Procedures, and preparations (eg, placement of the electrode montage and pulse oximeter). (revised per Amendment 01)

Subjects who continue to meet the eligibility criteria will remain overnight in the sleep laboratory. The median habitual bedtime (MHB) will be calculated from the most recent 5 days of the subject's sleep diary, and used to determine bedtime ("lights off"). The PSG recording will begin at lights off

and will continue for 8 hours (until lights on). The end of the 8-hour PSG recording will be defined as waketime (“lights on”). Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

The PSG recording will be reviewed for exclusion criteria related to obstructive sleep apnea (for the HV Cohort) and to moderate or severe obstructive sleep apnea (for the OSA Cohort), periodic limb movement disorder (PLMD), and parasomnias. The pulse oximetry recording will be reviewed for exclusion criteria related to oxygen desaturation. Subjects who continue to meet the eligibility criteria will enter the Baseline Period.

Baseline Period

For both cohorts, the Baseline day is also Day 1 of the Treatment Period. At the Baseline Period, subjects will be admitted to the clinic, and blood and urine samples will be collected for routine safety assessments. An ECG and urine drug test and breath alcohol test will be performed, and vital signs will be assessed. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered. Females of childbearing potential will undergo a urine pregnancy test.

Randomization Phase – HV Cohort

Treatment Period

For the HV Cohort, subjects who continue to meet the eligibility criteria will be randomized to treatment sequence A, B or C consisting of 3 Treatment Periods, 1-night duration each. Randomization will be stratified by age (to be specified in the Statistical Analysis Plan [SAP]). Within each age stratum, subjects will be randomized to 1 of the 3 treatment sequences. Each treatment sequence will be a different ordering of treatment administration. The study treatments will be lemborexant 10 mg, lemborexant 25 mg, and placebo.

At Treatment Period 1, subjects will enter the sleep laboratory and remain there overnight, where bedtime (lights off) will occur at the MHB determined at Screening Visit 2. Female subjects of childbearing potential will have a urine pregnancy test, and all subjects will have a urine drug test and breath alcohol test upon entry to the sleep laboratory. Subjects will be administered their assigned dose of study drug immediately (within 5 minutes) before lights off. The PSG recording will begin at lights off and will continue for 8 hours (until lights on). The following morning, a blood sample for pharmacokinetic (PK) assessment will be collected and vital signs assessed, as indicated in the Schedule of Procedures/Assessments. Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

Treatment Period 1 will be followed by Treatment Periods 2 and 3, with each treatment separated from the next by a washout of at least 14 days. Each period will follow the same procedures and assessments as Treatment Period 1.

Follow-Up Period

Following Treatment Period 3, a 14-day Follow-Up Period will begin immediately. Subjects will not receive any treatment during the Follow-Up and will return to the clinic after at least 14 days following the treatment period for an EOS Visit at which safety will be assessed, including AEs, 12-lead ECG, vital signs, weight, clinical hematology and blood chemistry laboratory evaluations, urine pregnancy test, urinalysis, and suicidality assessed by the C-SSRS. If subjects discontinue prematurely, they will undergo an Early Termination (ET) Visit and will be followed for at least 14 days, after which, an EOS visit should be scheduled.

Randomization Phase - OSA Cohort

Treatment Period

Subjects who continue to meet the eligibility criteria after the Baseline Visit will be randomized to treatment sequences D or E consisting of 2 Treatment Periods, 8 nights duration each.

Randomization will be stratified by age. Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio. Subjects will then enter Treatment Period 1. Treatments administered will be lemborexant 10 mg followed by placebo or placebo followed by lemborexant 10 mg, with the treatment periods separated by a washout interval of at least 14 days.

Subjects will remain overnight in the sleep laboratory. Bedtime (lights off) will be the MHB that was determined at Screening Visit 2. Subjects will receive study drug immediately (within 5 minutes) before lights off. The PSG recording will begin at lights off and will continue for 8 hours (until lights on). The following morning, a blood sample for PK assessment will be collected and vital signs assessed, as indicated in the Schedule of Procedures/Assessments. A single PK sample will be collected predose in Period 2 and within 1 hour of awakening in both Periods. Subjects will be provided with study drug to be administered for 6 consecutive nights at home, and will be instructed to take the medication immediately (within 5 minutes) before bedtime. If SpO₂ <80% for ≥20% of TST during the first night of treatment, the subject must be discontinued. Subjects may leave the clinic after the investigator determines that it is safe for them to do so. Subjects will be instructed to promptly contact the investigator in case of any new complaints or exacerbation of current symptoms.

On Day 5 (with a window of ±2 days), the site will telephone the subject to assess AEs and record concomitant medications. If any AE is clinically significant and requires follow-up, an Unscheduled Visit should be arranged as soon as possible.

After 6 consecutive nights of administering study drug at home, subjects will return to the clinic to remain overnight in the sleep laboratory for a PSG assessment. Subjects will undergo measurement of vital signs, urine pregnancy test for female subjects of childbearing potential, and urine drug and breath alcohol tests prior to the start of the PSG. Study drug will be administered immediately prior to the MHB (ie, within 5 minutes). In addition a blood sample for pre-dose (trough) PK will be taken within 1 hour before dosing. The following morning, a PK blood sample will be collected. Subjects will be instructed on study restrictions related to prohibited medications/drugs, alcohol and caffeine, and the prohibitions regarding the use of continuous positive airway pressure (CPAP) device or dental appliance. Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

After Treatment Period 1, there will be a washout interval of at least 14 days. After the washout interval, subjects will return to the clinic for Treatment Period 2, which will follow the same schedule and procedures as did Treatment Period 1.

Follow-Up Period

When the subject is discharged from the clinic after Treatment Period 2, the Follow-Up Period will begin. The Follow-Up Period will have a duration of at least 14 days, during which the subjects will not receive any study treatment. At the end of the Follow-Up Period, subjects will return to the clinic for an EOS visit at which safety will be assessed including adverse events, 12-lead ECGs, vital signs, weight, clinical hematology and blood chemistry labs, urine pregnancy test, and suicidality assessed by the C-SSRS. If subjects discontinue prematurely, they will undergo an ET Visit and will then be followed for at least 14 days, after which, an EOS visit should be scheduled.

Adjudication Committee

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

HV Cohort: A sufficient number of subjects will be screened in order to ensure that a total of 12 evaluable subjects complete the study (8 evaluable adult subjects [<65 years] and 4 evaluable elderly subjects [≥ 65 years]). Discontinued subjects may be replaced to ensure 8 adult subjects and 4 elderly subjects complete all 3 Treatment Periods.

OSA Cohort: A sufficient number of subjects will be screened in order to ensure that a total of 30 evaluable subjects complete the study (20 evaluable adult subjects [<65 years] and 10 evaluable elderly subjects [≥ 65 years]). Discontinued subjects may be replaced to ensure 20 adults and 10 elderly subjects complete both Treatment Periods.

Inclusion Criteria (HV and OSA Cohorts)

1. Male or female, age ≥ 18 years and ≤ 90 years at the time of informed consent
2. Voluntary agreement and ability to provide written informed consent
3. Reports habitually sleeping for at least 5.5 hours per night
4. Agrees to stay in bed for 7 hours per night for the duration of treatment.
5. Reports habitual bedtime between 21:00 and 01:00
6. $SpO_2 \geq 94\%$ assessed as part of vital signs at Screening Visit 1

Additional Inclusion Criteria (HV Cohort)

7. Body mass index (BMI) ≤ 32 kg/m²
8. On Screening PSG (Screening Visit 2) AHI < 5

Additional Inclusion Criteria (OSA Cohort)

9. BMI ≤ 40 kg/m²
10. Obstructive sleep apnea, diagnosed according to the criteria of the International Classification of Sleep Disorders, version 3 (ICSD-3)
11. On Screening PSG: AHI ≥ 5 to < 15 (mild severity)

Exclusion Criteria (HV and OSA Cohorts)

1. A current diagnosis of restless legs syndrome, PLMD, circadian rhythm sleep disorder, or narcolepsy
2. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicate the need for referral for a diagnostic evaluation for the presence of narcolepsy
3. A history of a parasomnia or parasomnia observed on the Screening PSG that in the investigator's opinion makes the subject unsuitable for the study
4. Periodic Limb Movement with Arousal Index (PLMAI) as measured on the Screening PSG:

- Age 18 to <65 years: PLMAI \geq 10
 - Age \geq 65 years: PLMAI >15
5. Females who are breastfeeding or pregnant. For females of childbearing potential, the serum beta-human chorionic gonadotropin (β -hCG) pregnancy test must be negative at Visit 1 and the urine pregnancy test must be negative at Screening Visit 2 and Baseline. An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
- Females of childbearing potential who, within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
- Total abstinence (if it is their preferred and usual lifestyle)
 - An intrauterine device or intrauterine hormone-releasing system (IUS)
 - A contraceptive implant
 - An oral contraceptive (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
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.
- NOTES: 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).
- It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
6. History of or suspected drug or alcohol use disorder within approximately 2 previous years
7. A positive drug test at Screening or Baseline, or unwilling to refrain from use of recreational drugs during the study
8. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), and unwilling to forego alcohol during the days prior to PSG recordings and to limit alcohol intake to no more than 2 alcohol-containing drinks per day (females) or 3 alcohol-containing drinks per day (males) on all non-PSG days for the duration of his/her participation in the study (NB: alcohol will not be permitted in the sleep laboratory).
9. Reports habitual caffeine use that is excessive in the opinion of the investigator. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and \geq 5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation. (revised per Amendment 01)
10. Known to be human immunodeficiency virus (HIV) positive

11. Active viral hepatitis (B or C) as demonstrated by positive viral serology at Screening
12. A prolonged QT/QTc interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated if initial ECG indicates a QTcF interval >450 ms) (revised per Amendment 01)
13. Comorbid nocturia resulting in the need to get out of bed to use the bathroom more than 3 times during the night
14. Any history of medical or psychiatric condition that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
15. Any suicidal ideation with intent to act with or without a plan, current or within 6 months before the C-SSRS administration during the Screening (e.g. answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS) (revised per Amendment 01)
16. Any suicidal behavior (per the Suicidal Behavior section of the C-SSRS) within 10 years of Screening (revised per Amendment 01)
17. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
18. Used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before the Screening PSG
19. Hypersensitivity to lemborexant or excipients
20. Currently enrolled in another interventional clinical trial or used any investigational drug or device within 30 days or 5 times the half-life, whichever is longer preceding informed consent
21. Previously participated in other clinical trial of lemborexant
22. Is unable to avoid working a night shift within 2 weeks before the Screening PSG, or between the Screening PSG and end of study
23. Has travelled across 3 or more time zones in the week prior to Screening, or plans to travel across 3 or more time zones during the study
24. Clinically significant findings based on vital signs, physical examination, ECG, or clinical laboratory tests (revised per Amendment 01)

Additional Exclusion Criteria (HV Cohort)

25. Any valid event of SpO₂ <90% during the Screening PSG
26. Current evidence of a clinically significant, active respiratory disorder. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease, or any other pulmonary disorder identified by review of medical history, physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments.
27. Presence of significant illness (including insomnia) that requires treatment or may influence the study assessments (e.g. psychiatric disorders, disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, cardiovascular system, or a congenital abnormality), malignancy within the past 5 years (other than adequately treated basal cell carcinoma or in situ carcinoma of the cervix), or chronic pain that in the opinion of the investigator could interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.

Additional Exclusion Criteria (OSA Cohort)

28. SpO₂ <80% for ≥ 5% of TST during the Screening PSG
29. Uses or plans to use CPAP device or dental appliance within 2 weeks of the Screening PSG (Screening Visit 2) or during the study
30. Current evidence of a clinically significant, active respiratory disorder other than OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history, physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments.
31. Current evidence of other clinically significant disease (e.g. psychiatric disorders, disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, cardiovascular system, or a congenital abnormality), malignancy within the past 5 years (other than adequately treated basal cell carcinoma or in situ carcinoma of the cervix), or chronic pain that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. Subjects with insomnia disorder, who complain of difficulties with sleep onset and/or sleep maintenance, are eligible provided that they meet this criterion. Note that medications to treat insomnia are prohibited; see the [appendices of the protocol](#).

Study Treatments

HV Cohort: lemborexant 10-mg film-coated tablets, lemborexant 25-mg dose consisting of 2 tablets of lemborexant 10 mg and 1 tablet of lemborexant 5 mg, lemborexant-matched placebo tablets. To maintain the blind, additional placebo tablets will be added in order to have in total 3 tablets administered during each Treatment Phase.

Study drug will be administered at bedtime in the clinic (within 5 minutes of lights off) in the evening of Day 1. Treatments will be administered orally with 240 mL (8 fluid ounces) of water.

OSA Cohort: lemborexant 10-mg film-coated tablets, lemborexant-matched placebo tablets

Study drug will be administered at bedtime in the clinic (within 5 minutes of lights off) in the evening of Days 1 and 8. On Days 2 to 7, subjects will take study drug at home, immediately (within 5 minutes) of the time they intend to try to sleep. Treatments will be administered orally with 240 mL (8 fluid ounces) of water.

Duration of Treatment

HV Cohort: A maximum of 3 days, comprising 3 Treatment Periods, each with a duration of 1 day

OSA Cohort: A maximum of 16 days, comprising 2 Treatment Periods, each with a duration of 8 days.

Concomitant Drug/Therapy (HV and OSA Cohorts)

OSA subjects will be required to abstain from using a CPAP device or dental appliance for at least 2 weeks before the Screening PSG, and throughout the study (until after the EOS Visit).

Subjects must abstain from the use of recreational drugs throughout the study. No alcohol will be permitted in the clinic.

Prohibited medications (see [appendices of the protocol](#)) should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before Screening Visit 2.

Prohibited medications include strong cytochrome P450 (CYP3A) inhibitors and all CYP3A inducers

as listed in the appendices to the protocol. Prohibited medications also include any pharmacological treatment for insomnia disorder, including any medications (hypnotics or medications with known sedating effects) that are used for the purpose of inducing sleep or for treating OSA. These prohibitions apply even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not specified as prohibited but is in the same class as a medication that is listed in appendices of the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

If a subject starts any prohibited medication or therapy, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study as listed in appendices to the protocol.

Assessments

Screening Assessments

Sleep Diary

A paper Sleep Diary will be completed within an hour of morning wake time on each morning of the Screening Period until the Screening PSG. This Sleep Diary will yield information on the MHB that will be used to determine eligibility, and to determine bedtime (lights off) in the clinic.

Efficacy Assessments

Not applicable.

Pharmacokinetic Assessments

A single blood sample for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be taken at predefined visits (see [Schedule of Procedures/Assessments](#)). The exact time and date of the most recent dose administered before each sample will be documented.

Safety Assessments

Safety assessments will include monitoring and recording all AEs; laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, including after the last dose of study drug, and at the EOS, ET and Unscheduled Visits.

C-SSRS

Suicidality will be assessed using the C-SSRS. The C-SSRS assesses an individual's degree of suicidality, including suicidal ideation and suicidal behavior.

Pharmacodynamic Assessments

PSG

Each PSG recording will include an electrode montage with electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), and ECG channels. In addition, the montage will include channels for recording respiratory variables including pulse oximetry. In addition, the Screening PSG will include channels for assessment of symptoms of periodic limb movement disorder.

Trained PSG scorers will score PSG records in 30-second epochs according to standard criteria. At Screening Visit 2, the PSG will be used to calculate AHI and PLMAI for evaluation of eligibility criteria. Subsequent PSGs will be used to determine:

- AHI: the number of apneas and hypopneas divided by the TST (in minutes) and multiplied by 60 (min / hour) (ie, the average number of apneas and hypopneas per hour of sleep), as defined by the American Academy of Sleep Medicine (respiratory safety/PD assessment)
- SpO₂ level
- REM/NREM stages (minutes and proportion from TST and time in bed)

Transmissive pulse oximetry is a noninvasive method for monitoring peripheral oxygen saturation (SpO₂). A sensor device is placed on a thin part of the subject's body; in the present study, this will be a fingertip. The device passes two wavelengths of light through the body part to a photodetector. This measures the changing absorbance at each of the wavelengths, allowing determination of the absorbance caused by the pulsing arterial blood alone, excluding venous blood, skin, bone, muscle and fat. The reading of oxygen saturation by pulse oximetry is not necessarily identical to the reading of arterial oxygen saturation (SaO₂) from (invasive) analysis of arterial blood gas, but the two are sufficiently correlated that pulse oximetry is valuable for measuring oxygen saturation in a clinical

setting, including in clinical trials.

Bioanalytical Methods

Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) will be measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay methods.

Statistical Methods

Details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

The following endpoints will compare lemborexant treatments with placebo:

Primary Endpoint (HV Cohort)

The mean SpO₂ during TST on Day 1 of treatment

Secondary Endpoints (HV Cohort)

1. The AHI on Day 1 of treatment
2. The percentage of TST during which SpO₂ is <90%, <85% and <80% on Day 1 of treatment
3. The proportion of subjects with at least one incident of SpO₂ <90% for at least 30 seconds during TST on Day 1 of treatment

Primary Endpoint (OSA Cohort)

The AHI on Day 8 of treatment

Secondary Endpoints (OSA Cohorts)

1. The AHI on Day 1 of treatment
2. The mean SpO₂ during TST on Day 1 and Day 8 of treatment
3. The percentage of TST during which the SpO₂ is <90%, <85% and <80% on Day 1 and Day 8 of treatment
4. The proportion of subjects with at least one incident of SpO₂ <90% for at least 30 seconds during TST on Day 1 and Day 8 of treatment.

Exploratory Endpoints (HV and OSA Cohorts)

1. The mean SpO₂ during REM sleep, NREM and wake
2. The AHI during REM and NREM sleep
3. The AHI separately for adult and elderly subjects at all days assessed
4. The mean SpO₂ during TST separately for adult and elderly subjects at all days assessed

Pharmacokinetic Endpoint (HV and OSA Cohorts)

Lemborexant and metabolites M4, M9 and M10 plasma concentrations

Pharmacokinetic/Pharmacodynamic (Exposure-Response) Endpoint (HV and OSA Cohorts)

Correlations between plasma concentrations of lemborexant and select pharmacodynamic variables including AHI, mean SpO₂ during TST, and proportion of TST in which SpO₂ is <90%, <85% and <80% at all days assessed.

Analysis Sets

Safety Analysis Set: Group of subjects who received study drug and have at least one postdose safety assessment.

Pharmacodynamic Analysis Set: The PD Analysis Set is the group of subjects who received at least 1

dose of study drug in all Treatment Periods and who had sufficient PD data to derive at least 1 primary PD parameter.

Pharmacokinetic Analysis Set: Group of subjects who have at least 1 quantifiable plasma concentration after dosing with lemborexant.

Efficacy Analyses

Not applicable

Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lemborexant and M4, M9 and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and M4, M9 and M10 plasma concentrations.

Pharmacodynamic Analyses

The following analyses will be performed on the PD Analysis Set for each cohort.

Analysis for the Primary Endpoint

HV Cohort: Mean SpO₂ during TST will be analyzed using a mixed effect model. The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: least squares (LS) means, difference in LS mean of lemborexant 10 mg and lemborexant 25 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided lower 95% CI) for the true mean difference (lemborexant – placebo) in SpO₂ and p-value. If the lower bound of the one-sided 95% CI of the treatment difference of SpO₂ is less than -5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO₂ compared to placebo.

OSA Cohort: AHI will be analyzed using a mixed effect model. The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: LS means, difference in LS mean of lemborexant 10 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided upper 95% CI) for the true mean difference (lemborexant – placebo) in AHI and p-value. If the upper bound of the one-sided 95% CI of the treatment difference of AHI is less than 5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant increase in AHI with mild OSA compared with placebo.

A sensitivity analysis may also be performed on the primary endpoint where outliers are excluded. Other sensitivity analyses may be explored.

Plots of AHI and SpO₂ treatment difference data (both individual and LS Mean) will be used to explore the results.

Analysis for the Secondary Endpoints

The continuous secondary endpoints will be analyzed using the same model as the primary endpoint. Treatment comparison will be performed using contrasts.

The proportion of subjects with SpO₂ <90% will be summarized using descriptive statistics. All analyses will be performed separately for each cohort.

Analysis for the Exploratory Endpoints

Summaries and plots of all endpoints may be produced for appropriate subgroups (eg age group, sex, BMI, race).

Subgroup analyses will also be performed as appropriate on primary and all secondary endpoints. All analyses will be performed separately for each cohort.

Pharmacokinetic/Pharmacodynamic (Exposure-Response) Analyses

The exposure-response (E-R) relationship between plasma concentrations of lemborexant after PSG, and selected PD parameters including but not limited to the respiratory safety variables (including AHI, mean SpO₂ during TST, and [proportion]of TST in which SpO₂ is <90%, <85%, and <80%) will be explored graphically. Any emergent relationship may be followed using population model-based analysis. The potential effect of covariates (eg, age) on the E-R relationship may be explored. The PK Analysis Set will be used for these assessments. All analyses will be performed separately for each cohort.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range markedly abnormal laboratory variables, out-of-range vital signs, and suicidality variables (C-SSRS) will be summarized using descriptive statistics. All analyses will be performed separately for each cohort.

Interim Analyses

No interim analysis is planned.

Sample Size Rationale

HV Cohort:

A mean difference of 5 percentage points between treatments in SpO₂ is considered to be clinically meaningful in a study of the respiratory safety of suvorexant in healthy adult volunteers (Uemura, et al., 2015). From that source, the within-subject variance is assumed to be 0.315%. With a total of 12 subjects (4 elderly and 8 adults) completing the study and assuming that the true difference between treatments is -1.0, there is 99% power that the lower bound of the 90% confidence interval for the difference in SpO₂ (lemborexant - placebo) would be greater than -5. Although the estimate of within-subject variability is based on a study of adult healthy volunteers, the addition of elderly subjects is expected to have a minimal effect on the combined variability and thus a minimal effect on the power.

OSA Cohort: A mean difference between treatments in AHI > 5 is considered clinically meaningful in studies of the respiratory safety of sleep agents in OSA (Sun, et al., 2016). The within-subject variance is assumed to be 25.34 for AHI for adult subjects (Sun, et al, 2016) and 30.41 for AHI for elderly subjects (where the elderly within-subject variance is estimated from adult data + 20%, Mitterling, et al, 2015; Lee, et al, 2016). Assuming the true difference in AHI (lemborexant – placebo) on Day 8 is as high as 1.5, a total of 30 subjects completing the study (20 adult, 10 elderly), provides 82% power that the upper bound of the 90% CI for the treatment difference in AHI (lemborexant – placebo) on Day 8 would be < 5.

Sample Size Estimates					
Description	Combined within-subject variance of AHI	Adult N	Elderly N	Total N	Total Power (%)
80% overall power with 20 adult subjects	26.96	20	10	30	82
85% overall power with 20 adult subjects	27.38	20	14	34	86
80% overall power with 20 elderly subjects	28.54	12	20	32	82

85% overall power with 20 elderly subjects	28.16	16	20	36	86
Equal number of subjects	27.875	20	20	40	90

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronym	Term
β-hCG	beta human-chorionic gonadotropin
AD-D	Alzheimer's Disease Dementia
AE	Adverse Event
AHI	apnea-hypopnea index
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
AUC _(0-inf)	area under the concentration-time curve from time zero to infinity
BMI	body mass index
BP	blood pressure
C-SSRS	Columbia – Suicide Severity Rating Scale
CFR	code of federal regulations
CI	confidence interval
CLIA	clinical laboratory improvement amendments
CPAP	continuous positive airway pressure
CRA	clinical research associate
CSR	clinical study report
CT	computed tomography
CV	curriculum vitae
CYP3A	cytochrome P450
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyography
EOG	electrooculography
EOS	end-of-study
ET	early termination
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
HV	healthy volunteers
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSD	International Classification of Sleep Disorders

Acronym	Term
IEC	internal ethics committee
IRB	Institutional Review Board
ISWRD	Irregular Sleep-Wake Rhythm Disorder
IUS	intrauterine hormone releasing system
KSS	Karolinska Sleepiness Scale
LC-MS/MS	liquid chromatography with-tandem mass spectrometry
LLT	lower level term
LS	least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MHB	median habitual bedtime
M-MSLT	modified multiple sleep onset latency test
NREM	non-rapid eye movement
OSA	obstructive sleep apnea
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
PLMAI	Periodic Limb Movement with Arousal Index
PLMD	Periodic Limb Movement Disorder
PSG	polysomnography
PT	Prerferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
REM	rapid eye movement
SAE	serious adverse event
SaO ₂	peripheral oxygen saturation
SAP	statistical analysis plan
SDLP	standard deviation of lateral position
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	standard operating procedure
TBD	to be decided
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
TST	total sleep time
WHO	World Hhealth Organization
WHO DD	World Health Organization Drug Dictionary
ZOP	zopiclone

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) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Federal Regulations, Title 21 CFR Part 56, for US studies). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate[s], change of telephone number[s]). Documentation of IRB 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 chairman must be sent to the principal investigator (PI) 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 decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRB annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, 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 of any reportable adverse events (AEs) per ICH guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB and US Food and Drug Administration (FDA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB and FDA 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 SOPs 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 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 Conference on Harmonisation of 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/desinee 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-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 approximately 10 investigational sites in the United States.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

Lemborexant (E2006) is a novel competitive dual orexin receptor antagonist that is under development for both insomnia disorder and irregular sleep-wake rhythm disorder (ISWRD).

Obstructive sleep apnea (OSA) is a common sleep disorder, characterized by intermittent cessation of airflow because of partial or complete occlusion of the upper airway during sleep. Repetitive collapse of the airway leads to sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, and increased sympathetic activity. Clinically, OSA is defined by excessive daytime sleepiness, loud snoring, witnessed apneas, or awakenings due to gasping or choking, in addition to at least 5 obstructive respiratory events per hour (Epstein, et al., 2009). The frequency of apneas and hypopneic episodes per hour of sleep is reported as an AHI; this evaluation requires overnight polysomnography (PSG). The International Classification of Sleep Disorders (ICSD) (American Academy of Sleep Medicine, 2014) defines the severity of OSA according to the AHI: an AHI ≥ 5 to <15 is classed as mild, AHI ≥ 15 to <30 as moderate, and AHI ≥ 30 as severe.

As a result of daytime sleepiness, patients with OSA are at increased risk of traffic accidents (Teran-Santos, et al., 1999). Further, OSA is associated with an increased incidence of hypertension, diabetes, cardiovascular and cerebrovascular disease (Bassetti, et al., 1996; Bassetti and Aldrich, 1999; Nieto, et al., 2000; Nieto, et al., 2009). Ventilation with continuous positive airway pressure (CPAP) is the gold-standard therapy. However, long-term compliance can be poor, with noncompliance rates as high as 50% by 1 year (Collen, et al., 2009).

Widely quoted figures for overall prevalence of OSA are 2% to 4% in the general adult population (Young, et al., 1993). However, the available estimates are likely to be lower than the true burden, because OSA is insidious, under-recognized and often undiagnosed (Young, et al., 1997). Particularly relevant to the lemborexant program in insomnia disorder is that OSA commonly coexists with insomnia; as many as 50% of subjects referred to a sleep clinic for sleep apnea have insomnia symptoms (Krakow, et al., 2001). Also highly relevant to the lemborexant programs in insomnia disorder is the fact that the prevalence of both OSA and insomnia increases with increasing age. Regarding insomnia, epidemiologic surveys reveal that more than 50% of adults over the age of 65 years have some form of chronic sleep-related complaints (Foley, et al., 1995), which often manifest as complaints of difficulty in falling asleep, and night-time awakenings (Ford and Kamerow, 1989). Regarding OSA, in a probability sample from two Pennsylvania counties, OSA prevalence was shown to increase progressively with age: in men, OSA (AHI >10) was present in 3.2%, 11.3%, and 18.1% of the 20- to 44-year, 45- to 64-year, and 61- to 100-year age groups, respectively (Bixler, et al., 1998; 2001). Further, and highly relevant to the lemborexant program in ISWRD, not only does Alzheimer Disease-Dementia (AD-D) tend to be a disease of old age, but signs and symptoms of sleep apnea are more common in patients with AD-D than in non-demented controls (Tractenberg, et al., 2005; 2006).

Even in healthy individuals, respiratory parameters during sleep tend to change with advancing decade of life, and to show deterioration after the age of 50 years; functioning continues to decline with age. For example, a recent study was conducted in 100 healthy sleepers age 19 to 77 years who had no diagnosis or suspicion of a sleep-related breathing disorder. Mean and minimal oxygen saturation decreased steadily after the age of 50 years, while mean AHI increased with each decade and showed a marked increase after the age of 60 years (Table 1; Mitterling, et al., 2015).

Table 1 AHI and Oxygen Saturation During Sleep by Decade of Life (Healthy Sleepers)

Respiratory parameter	Decade of life					P-value
	< 30 years	31–40 years	41–50 years	51–60 years	> 60 years	
n	20	21	15	15	24	
AHI (median and range)	0.5 (0.0–8.8)	1.0 (0.0–22.5)	1.9 (0.0–18.4)	2.6 (0.0–22.6)	6.6 (0.6–25.0)	< 0.001
Mean oxygen saturation%	95.2 (93.0–97.5)	95.5 (92.5–98.0)	95.0 (90.0–98.0)	93.8 (91.0–96.3)	93.5 (89.3–96.6)	0.001
Minimal oxygen saturation%	90.0 (84.0–95.0)	91.0 (86.0–95.0)	89.5 (81.0–94.0)	88.0 (78.0–93.0)	87.0 (80.0–98.0)	0.014

Data are shown as median and range.

AHI = apnea-hypopnea index.

Data from Mitterling, et al., 2015.

Given the changes in respiratory function with age even in healthy individuals, the increasing prevalence of both insomnia and OSA with age, and the coexistence of the 2 conditions in many patients, it is important to examine the safety in OSA of agents that are under development for sleep disorders.

7.1 Lemborexant

7.1.1 Lemborexant and Respiratory Function

In the multiple ascending dose (MAD) study (E2006-A001-002; Study 002), which recruited adults and elderly subjects, a continuous finger pulse oximetry channel ran for 12.5 hours each night of 14 nights of dosing. The peripheral oxygen saturation (SpO₂) signal would alarm if SpO₂ dropped below 92%. There was no PSG. The alarm signalled for 3 subjects, 2 of whom received lemborexant 25 mg while the other received placebo. All 3 subjects experienced desaturations below 80%, the level that is considered clinically significant hypoxia. No subject experienced hypoxia during screening or pre-dose on study nights.

The subject dosed with placebo was a 69-year-old Japanese male. On Days 3, 4, 7 and 9 he experienced episodes of desaturation that triggered the alarm. On each of these days his SpO₂ dipped below 80%, each episode lasting between a few seconds and 2 minutes. His lowest value for SpO₂ was 77% (for a few seconds). There was no consistent pattern regarding the timing of these events during the night.

The first subject dosed with lemborexant 25 mg with an event was a 76-year-old white male. On Days 1, 2, 3, 4, 5, 6, 8, 9 and 10, he experienced desaturations that triggered the alarm. On Days 1, 2, 3, 4 and 10, his SpO₂ dipped below 80% for a few seconds, usually returning to the mid-80% for several minutes before the event resolved. His lowest value for SpO₂ was 75% (for a few seconds). There was no consistent pattern regarding the timing of these events during the night.

The second subject dosed with lemborexant 25 mg with an event was a 66-year-old white male. On Day 6, his SpO₂ fell to 76% for about a minute before rising to 82% for a few minutes, after which the event resolved. On Day 13 he experienced “hypoxemia” for a few seconds (no quantitative data are available).

7.1.2 Mechanism of Action

Lemborexant, E2006, (1R,2S)-2-{{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide belongs to the pharmacologic class of orexin receptor antagonists.

Orexin neuropeptides (orexin-A and orexin-B) have been recognized as critical upstream controllers of most wake-promoting neurotransmitters via two G protein-coupled receptors, the orexin-1 receptor and the orexin-2 receptor. Small-molecule antagonists of orexin receptors, such as suvorexant, have recently emerged as a new class of chemical compounds that represents a novel alternative approach to treat insomnia disorder.

7.1.3 Clinical Experience With Lemborexant

7.1.3.1 Phase 1

E2006-A001-001 (Study 001): Single ascending dose study. This study included healthy subjects and otherwise healthy subjects with primary insomnia. In addition to determining the safety and tolerability of single doses, the study provided preliminary evidence of efficacy in the target patient population.

E2006-A001-002 (Study 002): Multiple ascending dose study. This study enrolled healthy adult and elderly subjects, each of whom was dosed with lemborexant or placebo at night. In addition to determining the safety and tolerability of multiple doses, the study also provided preliminary evidence of a lack of important differences in exposure between adult and elderly subjects.

E2006-A001-003 (Study 003): A multiple dose study to bridge pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability between Japanese and white healthy subjects. This study provided evidence of a lack of important differences in exposure and safety between Japanese and white subjects.

E2006-A001-004 (Study 004): Metabolism-based inducer/inhibitor study. This study provided data demonstrating (1) strong inhibitors of cytochrome P450 (CYP3A) lead to

higher plasma concentrations of lemborexant; and (2) strong inducers of CYP3A lead to notably lower plasma concentrations of lemborexant. The study also demonstrated a weak effect of lemborexant on CYP2B6 activity and no effect on CYP3A activity.

E2006-A001-005 (Study 005): Relative bioavailability study of capsules vs tablet formulations. This study demonstrated that the capsules and tablets provided similar exposure (maximum observed concentration [C_{max}] and area under the concentration-time curve [AUC]), thus allowing the tablet formulation to be used in future clinical trials.

E2006-A001-007 (Study 007): Human mass balance absorption, distribution, metabolism, and excretion study to characterize the route and extent of excretion of lemborexant. This study demonstrated that elimination takes place by fecal (57%) and urinary excretion (29%) based on total recovery (86.5%) of radioactivity following a single dose of radiolabeled lemborexant. In addition, there were no human-specific metabolites and the only major (12%) metabolite was M10. The blood-to-plasma ratio was approximately 0.65.

E2006-A001-008 (Study 008): Food effect study. This study demonstrated a mild food effect. The C_{max} was decreased by 23% and the AUC from zero time zero to infinity (AUC[0-inf]) was increased by 18% following consumption of a high fat meal.

E2006-E044-106 (Study 106) was a randomized, double-blind, placebo-controlled, 4-way incomplete block crossover study in healthy volunteers to evaluate on-road driving safety. The primary objective was to demonstrate that lemborexant 2.5, 5, and 10 mg compared to placebo does not impair driving as assessed by standard deviation of lateral position (SDLP) during an on-road driving test in the morning following a single dose (Day 2) and multiple doses (Day 9) of lemborexant administered at bedtime. An active comparator, zopiclone 7.5 mg (ZOP) was included for assay sensitivity. All subjects received placebo and ZOP, and 2 of the 3 lemborexant doses. A total of 48 subjects were randomized and completed all 4 treatment periods; no subject discontinued from the study. No drives were stopped or never started while subjects were taking lemborexant; 3 drives from 2 subjects were stopped when subjects were taking ZOP. The primary objective was met, ie, for drives on both Day 2 and Day 9, for all lemborexant doses, the upper bound of the 95% CI for SDLP treatment difference from placebo did not exceed the prespecified clinically meaningful threshold of 2.4 cm. Symmetry analyses were not statistically significant for any lemborexant dose at either Day 2 or Day 9, indicating that the frequency of subjects with SDLP treatment difference from placebo ≥ 2.4 cm (impaired) was similar to the frequency of subjects with SDLP treatment difference from placebo ≤ -2.4 cm (improved). Assay sensitivity was demonstrated: for ZOP, the upper bound of the 95% CI of SDLP treatment difference from placebo exceeded 2.4 cm (Days 2 and 9), and the symmetry analyses for ZOP were statistically significant (Days 2 and 9).

E2006-A001-107 (Study 107): This Phase 1 study was conducted to evaluate the effects of the 5 and 10 mg doses on next-morning residual sleepiness in subjects with insomnia disorder. The study design was randomized, double-blind, and placebo-controlled with a 3-way crossover. Next-morning residual sleepiness was measured on a modified multiple sleep

onset latency test (M-MSLT). An active comparator, flurazepam 30 mg, was included to confirm assay sensitivity. Results showed that for neither 5 mg nor 10 mg was the lower bound of the 95% confidence interval (CI) of the treatment difference in change from baseline of average sleep onset latency on the M-MSLT more than -6 minutes, which was the prespecified criterion defining clinically meaningful next-morning residual sleepiness. That is, neither dose level of E2006 resulted in a clinically meaningful reduction in average time to sleep onset in the morning hours, supporting the safety of these doses and their use in Phase 3 studies.

7.1.3.2 Phase 2

A dose-finding study (E2006-G000-201; Study 201) was conducted in subjects who had insomnia disorder, with the primary objectives of identifying doses that resulted in efficacy but did not result in significant next-day residual sleepiness. The doses evaluated were 1, 2.5, 5, 10, 15, and 25 mg, administered once daily for 15 days. The study was stopped early for efficacy after the prespecified success criterion for sleep efficiency (SE) was achieved without unacceptable next-day residual sleepiness as evaluated by the Karolinska Sleepiness Scale (KSS).

As measured by PSG, improvements in sleep were also demonstrated by statistically significant increases from baseline in SE, and by decreases from baseline in mean latency to persistent sleep and wake after sleep onset. These changes were largely maintained over 15 days of treatment with lemborexant as compared with placebo. Subjective measures derived from sleep diary entries yielded results largely comparable to PSG-derived results. Further, there was no evidence of rebound insomnia after treatment was completed, as measured either by PSG or sleep diary.

At doses up to 10 mg, changes from baseline in next-day sleepiness, as measured by the KSS, did not differ from those after placebo. At the highest doses of 15 and 25 mg, the increase in KSS from baseline was statistically significantly different from placebo at some time points, but the increases in KSS were of small magnitude (ie, less than 1 unit on average). Although there was approximately a one- to two-fold accumulation of lemborexant in plasma over the 15-day Treatment Period across the dose range, next-day sleepiness did not increase from the beginning to the end of treatment.

7.2 Study Rationale

Sedative hypnotics represent the main pharmacologic therapy for insomnia. Benzodiazepines used as sedative hypnotics (eg, triazolam, flurazepam) bind to the benzodiazepine receptor at the gamma-amino butyric acid-A (GABA-A) complex; concerns have been raised that this mechanism of action might be associated with depression of central respiratory drive, blunting of the arousal response to hypoxia, and decreases in muscle tone in the upper airways (Guilleminault, 1990; Berry, et al., 1995; George, 2000), thereby exacerbating the symptoms of OSA. Limited data are available regarding the use of the newer nonbenzodiazepine receptor agonists (the “z-drugs”: zolpidem, zaleplon, zopiclone, and eszopiclone) in patients with OSA. The US label for Ambien® (zolpidem) includes a statement

that Ambien[®] should be “used with caution in patients with sleep apnea syndrome.” Regarding eszopiclone (Lunesta[®]), some researchers have reported an improvement in some aspects of respiration in patients with OSA (Eckert, et al., 2011). However, the US label for Lunesta, though not specifically mentioning OSA, includes a statement that caution is advised if Lunesta is prescribed to patients with compromised respiratory function.

Effects of suvorexant (Belsomra[®]) on respiratory function have been studied in healthy subjects (Uemura, et al., 2015). The primary assessment was of mean changes in oxygen saturation measured by pulse oximetry (SpO₂) while secondary endpoints included the mean change from baseline in AHI. Single doses of suvorexant (40 mg and 150 mg) did not produce a clinically significant reduction of mean SpO₂ during total sleep time (TST) in healthy subjects, compared with placebo. And there was no significant difference identified between suvorexant and placebo for mean change from baseline in AHI.

Both ramelteon (Rozarem[®]) and suvorexant (Belsomra[®]) have been tested in subjects with OSA. Single doses of ramelteon (16 mg; twice the recommended dose in insomnia) were compared with placebo in a 2-period crossover design in 26 non-elderly subjects with mild or moderate OSA (Kryger, et al., 2007). The effects on respiration were assessed by mean changes in AHI and in SpO₂. Ramelteon did not worsen OSA. However, the fact that only single doses were tested is reflected in the language of the US label: “There is no available information on the respiratory effects of multiple doses of Rozerem in patients with sleep apnea. The effects on exacerbation in patients with mild to moderate sleep apnea cannot be definitively known from this study.” The only study of ramelteon in elderly subjects with OSA was a pilot study that primarily assessed the effects on insomnia (Gooneratne, et al., 2010). This report concluded that further research would be warranted in examining the role of ramelteon in older adults with insomnia symptoms and sleep apnea.

Merck conducted a 2-period-crossover study to assess the effects on respiration of suvorexant 40 mg (when dosed to steady state) compared with placebo in 26 non-elderly subjects with mild or moderate OSA (Sun, et al., 2016). As with ramelteon, the primary assessment was of mean changes in the AHI while secondary endpoints included oxygen saturation measured by pulse oximetry (SpO₂). Although 40 mg suvorexant is twice the maximum recommended dose in the US, at the time the study was initiated, Merck had intended that 40 mg be approved as the maximum dose. The study met its primary objective (see also below; Justification of the Sample Size). However, there were 8 (of a total of 25) evaluable subjects whose AHI at the end of the treatment period with suvorexant was ≥ 5 higher (worse) than the corresponding value after placebo. Five of these 8 subjects had a similar treatment difference in AHI on the first night of dosing. There was also wide variability in the data. The US label includes the following language: “There was wide inter- and intra-individual variability such that clinically meaningful respiratory effects of Belsomra in obstructive sleep apnea cannot be excluded.” Suvorexant has not been studied in OSA in subjects older than 64 years.

The prevalence of sleep-related difficulties, including insomnia and OSA, increases with age. Given the increased prevalence of OSA, insomnia and AD-D with age, it is important that

lemborexant be studied in both adult and elderly patients with OSA. Study 102 is designed to assess the effects of lemborexant in subjects with mild OSA, and will recruit adult and elderly subjects up to the age of 90 years.

8 STUDY OBJECTIVES

8.1 Primary Objectives

8.1.1 HV

The primary objective of the study for the healthy volunteers (HV) cohort is to determine whether lemborexant decreases the peripheral oxygen saturation (SpO₂) during total sleep time (TST) in healthy adults and elderly subjects after a single dose of treatment compared with placebo.

8.1.2 OSA

The primary objective of the study for the OSA cohort is to determine using PSG, whether lemborexant increases the AHI after multiple doses of treatment in adult and elderly subjects with mild OSA compared with placebo.

8.2 Secondary Objectives

8.2.1 HV

The secondary objectives of the study for the HV cohort are:

1. Determine whether lemborexant increases the apnea-hypopnea index (AHI) after a single dose of treatment compared with placebo
2. Determine whether lemborexant decreases SpO₂ during TST below defined thresholds after a single dose of treatment compared with placebo (revised per Amendment 01)
3. Evaluate safety and tolerability of lemborexant

8.2.2 OSA

The secondary objectives of the study for the OSA cohort are:

1. Determine whether lemborexant increases the AHI after the first dose of treatment compared with placebo
2. Determine whether lemborexant decreases the mean SpO₂ during TST after the first and after multiple doses of treatment compared with placebo
3. Determine whether lemborexant decreases SpO₂ during TST below defined thresholds after the first and after multiple doses of treatment compared with placebo
4. Evaluate safety and tolerability of lemborexant

8.3 Exploratory Objectives (HV and OSA Cohorts)

Explore the effects of lemborexant compared with placebo after a single dose in HV Cohort and after the first and multiple doses in the OSA Cohort on the following:

1. The mean SpO₂ during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
2. AHI during REM and NREM sleep
3. AHI separately for adult and elderly subjects
4. The mean SpO₂ during TST separately for adult and elderly subjects

In addition, explore the following for both HV and OSA Cohorts:

1. Plasma concentrations of lemborexant and metabolites M4, M9 and M10
2. Exposure-response (E-R) relationships between lemborexant concentrations and pharmacodynamic (PD) variables, including but not limited to respiratory safety variables (AHI, mean SpO₂ during TST, proportion of TST during which the SpO₂ is decreased below defined thresholds)

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-A001-102 is a multicenter, multiple dose, randomized, double-blind, placebo-controlled, crossover study in adult and elderly healthy subjects and adult and elderly subjects with mild Obstructive Sleep Apnea.

Study 102 will consist of 2 cohorts: healthy subjects and subjects with mild OSA. The design of the study is based on the studies conducted with suvorexant in healthy volunteers and subjects with OSA.

9.1.1 Healthy Volunteer Cohort

In the HV Cohort, this will be a single dose, randomized, double-blind, placebo-controlled, 3-period crossover study, with the primary endpoint of mean SpO₂ during total sleep time. There will be 2 phases, Prerandomization and Randomization. The Prerandomization Phase will last up to 21 days and will consist of the Screening Period and Baseline Period. The Baseline Period will last less than 1 day, and is on the same day as the Treatment Period 1, Study Day 1.

Eligible healthy adult and elderly subjects will be randomized to treatment sequence A, B or C (see [Table 2](#)), each consisting of 3 Treatment Periods, each of one night's duration, in

which subjects will receive a single dose of lemborexant 10 mg, or lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. When the subject is discharged from the clinic after Treatment Period 3, the Follow-Up Period will begin. The Follow-Up Period will have a duration of at least 14 days, during which the subjects will not receive any treatment. At the end of the Follow-up Period, there will be an End of Study (EOS) Visit. If subjects discontinue prematurely, they will undergo an Early Termination (ET) Visit and will then be followed for at least 14 days, after which, an EOS visit should be scheduled. A sufficient number of subjects will be randomized to ensure that 8 evaluable adult subjects (<65 years) and 4 evaluable elderly subjects (≥65 years) complete the study. An evaluable subject is defined as having SpO₂ readable for >90% of PSG recording for every Treatment Period.

9.1.1.1 Prerandomization Phase (HV Cohort)

The Prerandomization Phase will last up to 21 days and will consist of a Screening Period and a Baseline Period.

At specified visits throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments, including 12-lead electrocardiograms (ECG), physical examination, vital signs, weight, height, hematology, blood clinical chemistry analysis, urinalysis, reporting of AEs, and assessment of suicidality. At each clinic visit, subjects will also undergo a urine drug test and breath alcohol test.

9.1.1.1.1 SCREENING PERIOD (HV COHORT)

The Screening Period will begin no more than 21 days before the subject is randomized. At the first Screening Visit, informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted. The medical history will include history of falls. Additional eligibility criteria will be assessed, and safety assessments will be conducted, as indicated in the Schedule of Procedures/Assessments; these will include the Columbia – Suicide Severity Rating Scale (C-SSRS). Female subjects of childbearing potential will undergo a serum pregnancy test. Subjects will undergo the following assessments during screening: demography, physical examination, viral serology, serum pregnancy test, urine drug test, breath alcohol test, height, weight, clinical labs, vital signs, ECG and concomitant medications.

Subjects will also be instructed regarding study restrictions pertaining to prohibited medications/drugs, alcohol and caffeine.

After at least 6 days (to allow subjects the opportunity to complete the sleep diary for at least 5 consecutive nights), subjects will return to the clinic for the second Screening Visit (Visit 2) to undergo polysomnography (PSG). On this and all other nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, scheduled assessments (including a urine drug test and

breath alcohol test) as described in the Schedule of Assessments/Procedures, and preparations (eg, placement of the electrode montage and pulse oximeter).

Subjects who continue to meet the eligibility criteria will remain overnight in the sleep laboratory. The median habitual bedtime (MHB) will be calculated from the most recent 5 days of the subject's sleep diary. This will be used to determine bedtime ("lights off") The PSG recording will begin at lights off and will continue for 8 hours (until lights on). The end of the 8-hour PSG recording will be defined as waketime ("lights on"). Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

The PSG will be reviewed for exclusion criteria related to OSA.

The pulse oximetry recording will be reviewed for exclusion criteria related to oxygen desaturation. Subjects who continue to meet the eligibility criteria will enter the Randomization Phase.

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 9.5.1.6.4](#).

9.1.1.1.2 BASELINE PERIOD (HV COHORT)

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](#)) will begin the Randomization Phase. Baseline assessments and timing thereof are shown in [Section 9.5.1.6.4](#).

A baseline period of <1 day duration will start after the Screening PSG have been reviewed for eligibility. Subjects will be admitted to the clinic. Blood and urine samples will be collected for routine safety assessment. An ECG, urine drug test, and breath alcohol test will be performed, and vital signs will be assessed. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered. Females of childbearing potential will undergo a urine pregnancy test.

9.1.1.2 Randomization Phase (HV Cohort)

Subjects who continue to meet the eligibility criteria will be randomized to treatment sequence A, B or C consisting of 3 Treatment Periods, 1-night duration each: lemborexant 10 mg, lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. Randomization will be stratified by age (<65 years vs. ≥ 65 years). Within each age stratum, subjects will be randomized to 1 of the 3 treatment sequences. Subjects will then enter Treatment Period 1. Procedures and assessments to be conducted during the Randomization Phase are detailed in [Table 5](#).

9.1.1.2.1 TREATMENT PERIODS (HV COHORT)

Treatment Period 1

Subjects will remain overnight in the sleep laboratory. A serum pregnancy test will be performed at Screening Visit 1 for women of childbearing potential; a urine pregnancy test will be performed at all other time points specified in the Schedule of Assessments and Procedures. A urine drug screen and a breath alcohol test will be performed at Screening Visits 1 and 2, and at the time points specified in the Schedule of Assessments and Procedures. Bedtime (lights off) will be at the median habitual bedtime (MHB) that was used at the second Screening Visit (Visit 2). Subjects will receive study drug immediately (within 5 minutes) before lights off. The PSG recording will begin at lights off and will continue for 8 hours (until lights on). Subjects will also be instructed on study restrictions related to prohibited medications/drugs, caffeine and alcohol. The following morning, a PK blood sample will be collected and vital signs assessed, as indicated in the Schedule of Procedures/Assessments. Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

After Treatment Period 1, there will be a washout interval of at least 14 days.

Treatment Period 2

After the washout interval, subjects will return to the clinic for Treatment Period 2, which will follow the same schedule and procedures as in Treatment Period 1 (including urine pregnancy test for female subjects of childbearing potential, urine drug test, and breath alcohol test). In addition, a blood sample for predose (trough) PK will be taken within 1 hour before dosing on the PSG night.

After Treatment Period 2, there will be a washout interval of at least 14 days.

Treatment Period 3

After the washout interval, subjects will return to the clinic for Treatment Period 3, which will follow the same schedule and procedures as did Treatment Period 1.

When the subject is discharged from the clinic after Treatment Period 3, the Follow-Up Period will begin immediately. The Follow-Up Period will have a duration of at least 14 days, during which the subjects will not receive any treatment. (revised per Amendment 01)

9.1.1.2.2 FOLLOW-UP PERIOD (HV COHORT)

At the end of the Follow-Up Period, subjects will return to the clinic for an EOS visit at which safety will be assessed including adverse events, 12-lead ECG, vital signs, weight, clinical labs as indicated in [Table 5](#), and suicidality assessed by the C-SSRS. If subjects discontinue prematurely, they will undergo an ET Visit and will then be followed for at least 14 days, after which, an EOS visit should be scheduled.

The Treatment Phase assessments and timing thereof are shown in [Section 9.5.1.6.4](#).

9.1.2 Obstructive Sleep Apnea (OSA Cohort)

In the OSA Cohort, this will be a randomized, double-blind, placebo-controlled, 2-period crossover study. Lemborexant will be compared with placebo, using for the primary endpoint the AHI on the last night of dosing (both treatment periods), and with secondary endpoints that assess oxygen saturation as SpO₂. As with the HV cohort, there will be 2 phases, Prerandomization and Randomization. The Prerandomization Phase will last up to 21 days and will consist of the Screening Period and Baseline Period. The Baseline Period will last less than 1 day, and is on the same day as the Treatment Period 1, Study Day 1.

At Baseline, subjects will undergo a screening PSG to confirm the diagnosis and severity of OSA. At specified visits throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety and pharmacodynamics assessments. Adult and elderly subjects with mild OSA will be randomized to treatment sequences D or E (see [Table 3](#)) each consisting of 2 Treatment Periods, each of 8 nights' duration, in which subjects will receive lemborexant 10 mg or placebo; the Treatment Periods will be separated by a washout interval of at least 14 days. When the subject is discharged from the clinic after Treatment Period 2, the Follow-Up Period will begin. The Follow-Up Period will have a duration of at least 14 days, during which the subjects will not receive any treatment. At the end of the Follow-Up Period, subjects will return to the clinic for an EOS visit. If subjects discontinue prematurely, they will undergo an Early Termination (ET) Visit and will then be followed for at least 14 days, after which, an EOS visit should be scheduled. A sufficient number of subjects will be randomized to ensure that 20 evaluable adult subjects (<65 years) and 10 evaluable elderly subjects (≥65 years) complete the study. An evaluable subject is defined as having AHI validly calculated from PSG recoding for every Treatment Period.

No interim analysis is planned.

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

An overview of the study design for the HV cohort and OSA cohort is presented in [Figure 1](#) and [Figure 2](#), respectively.

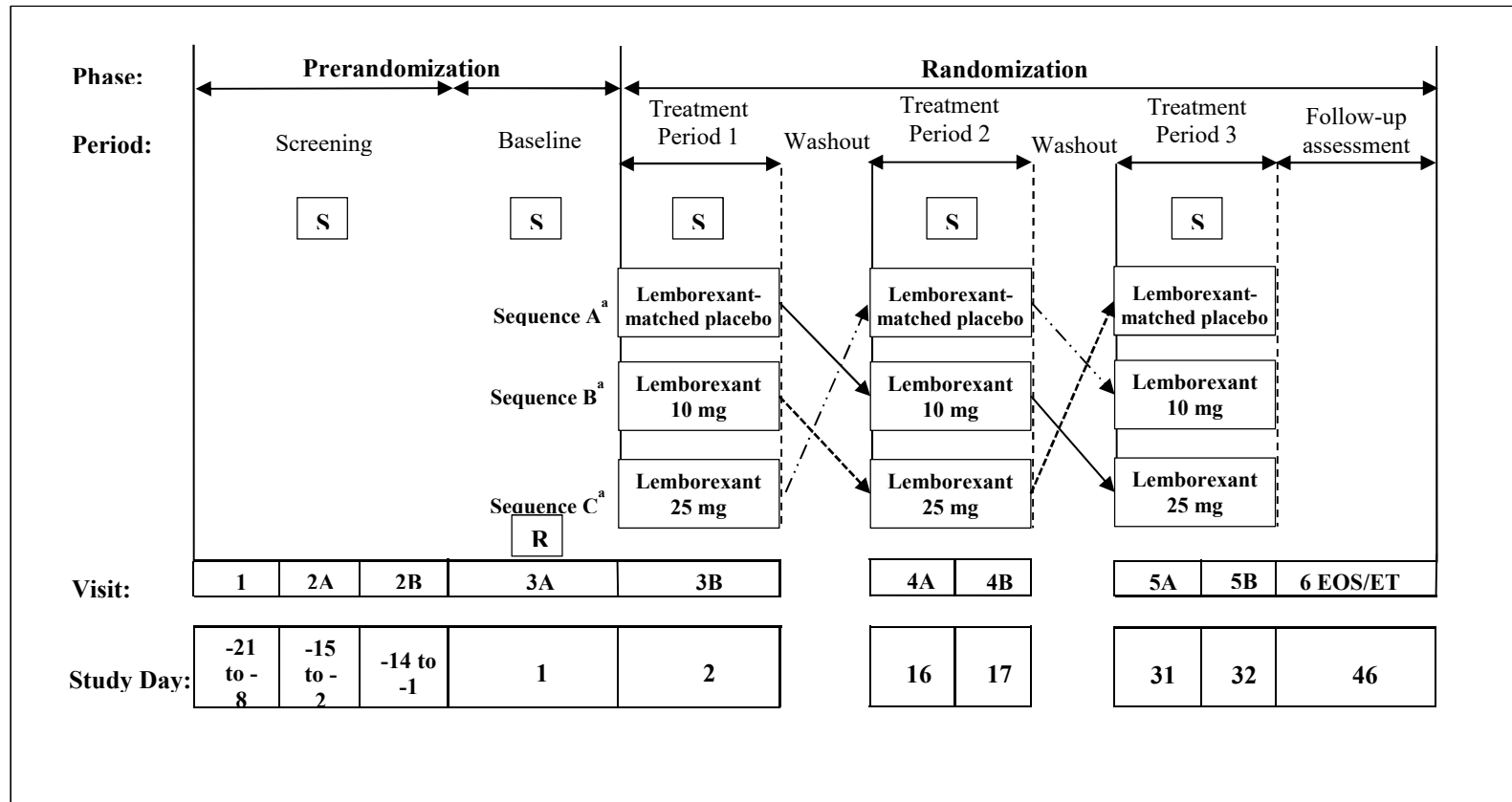


Figure 1 Study Design for HV Cohort

EOS = End of Study, ET = Early Termination Visit, S = Sleep Laboratory, R = randomization.

^a. Sequence A = placebo (Period 1), lemborexant 10 mg (Period 2), and lemborexant 25 mg (Period 3)

Sequence B = lemborexant 10 mg (Period 1), lemborexant 25 mg (Period 2), and placebo (Period 3)

Sequence C = lemborexant 25 mg (Period 1), placebo (Period 2), and lemborexant 10 mg (Period 1)

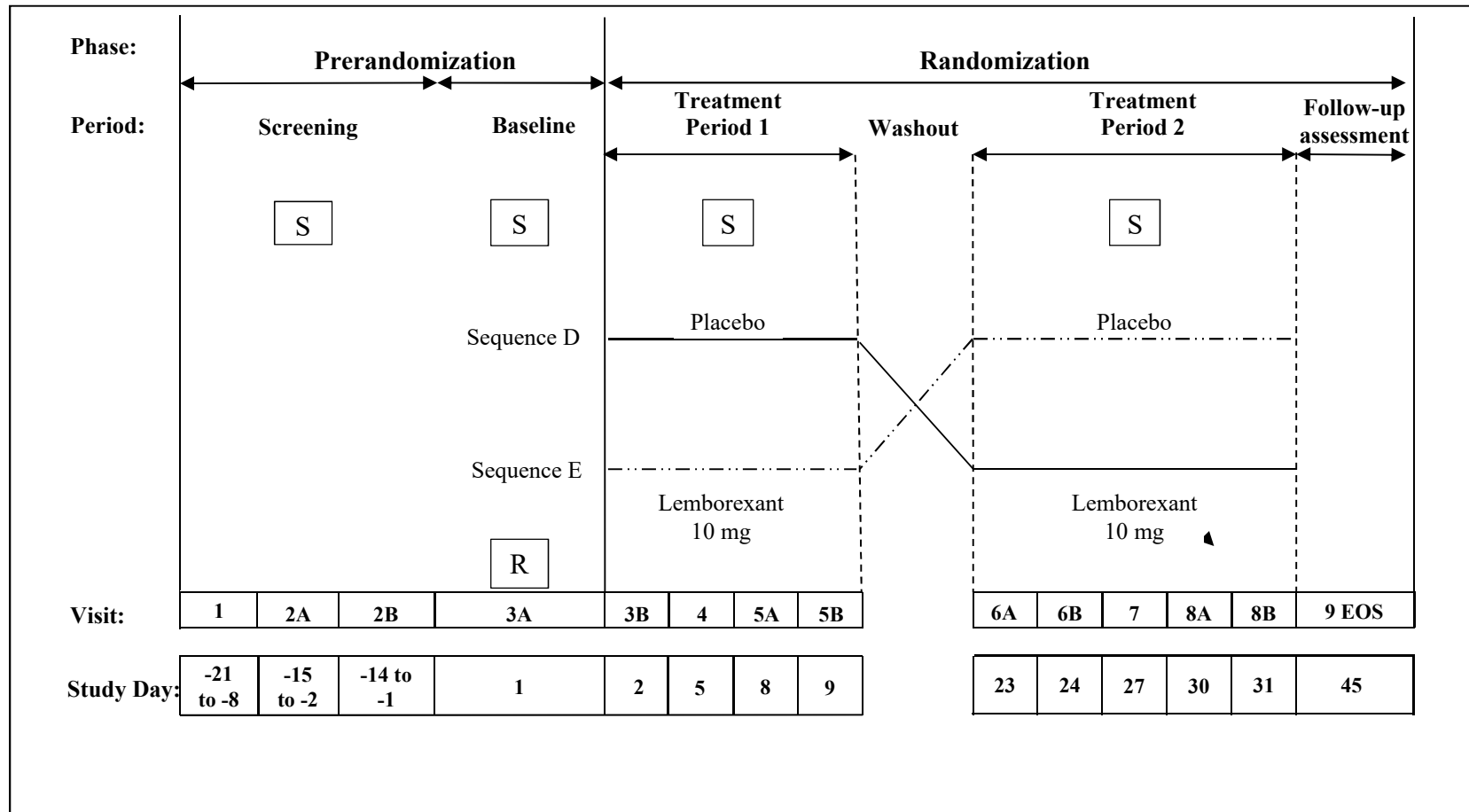


Figure 2 Study Design for OSA Cohort

EOS = End of Study, S = Sleep Laboratory, R = randomization

Sequence D = Placebo (Period 1), Lemborexant 10 mg (Period 2); Sequence E = Lemborexant 10 mg (Period 1), Placebo (Period 2).

9.1.2.1 Prerandomization Phase (OSA Cohort)

The Prerandomization Phase for the OSA Cohort will last up to 21 days and will consist of a Screening Period and a Baseline Period.

At specified visits throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments, including 12-lead electrocardiograms (ECG), physical examination, vital signs, weight, height, hematology, blood clinical chemistry analysis, urinalysis, reporting of adverse events (AEs), and assessment of suicidality. At each clinic visit, subjects will also undergo a urine drug test and breath alcohol test.

9.1.2.1.1 SCREENING PERIOD (OSA COHORT)

The Screening Period will begin no more than 21 days before the subject is randomized. At the first Screening Visit, informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted. The medical history will include history of falls. Additional eligibility criteria will be assessed, and safety assessments will be conducted, as indicated in the Schedule of Procedures/Assessments; these will include the Columbia – Suicide Severity Rating Scale (C-SSRS). Female subjects of childbearing potential will undergo a serum pregnancy test. Subjects will undergo the following assessments during screening: demography, physical examination, viral serology, serum pregnancy test, urine drug test, breath alcohol test, height, weight, clinical labs, VS, ECG and concomitant medications.

Subjects will also be instructed regarding study restrictions pertaining to prohibited medications/drugs, alcohol and caffeine.

After at least 6 days (to allow subjects the opportunity to complete the sleep diary for at least 5 consecutive nights), subjects will return to the clinic for the second Screening Visit (Visit 2) to undergo polysomnography (PSG). On this and all other nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, scheduled assessments (including a urine drug test and breath alcohol test) as described in the Schedule of Assessments/Procedures, and preparations (eg, placement of the electrode montage and pulse oximeter).

Subjects who continue to meet the eligibility criteria will remain overnight in the sleep laboratory. The median habitual bedtime (MHB) will be calculated from the most recent 5 days of the subject's sleep diary. This will be used to determine bedtime ("lights off") The PSG recording will begin at lights off and will continue for 8 hours (until lights on). The end of the 8-hour PSG recording will be defined as waketime ("lights on"). Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

The PSG will be reviewed for exclusion criteria related to OSA moderate or severe OSA, periodic limb movement disorder, and parasomnias.

The pulse oximetry recording will be reviewed for exclusion criteria related to oxygen desaturation. Subjects who continue to meet the eligibility criteria will enter the Randomization Phase.

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 9.5.1.6.4](#).

9.1.2.1.2 BASELINE PERIOD (OSA COHORT)

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](#)) will begin the Randomization Phase. Baseline assessments and timing thereof are shown in [Section 9.5.1.6.4](#).

A baseline period of <1 day duration will start after the Screening PSG have been reviewed for eligibility. Subjects will be admitted to the clinic. Blood and urine samples will be collected for routine safety assessment. An ECG, urine drug test, and breath alcohol test will be performed, and vital signs will be assessed. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered. Females of childbearing potential will undergo a urine pregnancy test.

9.1.2.2 Randomization Phase (OSA Cohort)

Subjects who continue to meet the eligibility criteria will be randomized in treatment sequences D or E consisting of 2 Treatment Periods, 8 nights duration each: lemborexant 10 mg and placebo, with the treatments periods separated by a washout interval of at least 14 days. Randomization will be stratified by age (<65 years vs ≥65 years). Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio. Subjects will then enter Treatment Period 1. Procedures and assessments to be conducted during the Randomization Phase are detailed in [Table 6](#).

9.1.2.2.1 TREATMENT PERIODS (OSA COHORT)

Subjects who continue to meet the eligibility criteria will be randomized in treatment sequences D or E consisting of 2 Treatment Periods, 8 nights duration each: lemborexant 10 mg and placebo, with the treatments periods separated by a washout interval of at least 14 days. Randomization will be stratified by age (<65 years vs ≥65 years). Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio.

Treatment Period 1

Subjects will remain overnight in the sleep laboratory. Subjects will undergo the following procedures at the Screening Visits 1 and 2 and on Day 1: urine pregnancy test for female subjects of childbearing potential, and for all subjects, a urine drug test and breath alcohol

test). Bedtime (lights off) will be at the MHB that was used at the second Screening Visit (Visit 2). Subjects will receive study drug immediately (within 5 minutes) before lights off. The PSG recording will begin at lights off and will continue for 8 hours (until lights on). The following morning, a PK blood sample will be collected and vital signs assessed, as indicated in the Schedule of Procedures/Assessments. Subjects will be provided with study drug to be administered for 6 consecutive nights at home, and will be instructed to take the medication immediately (within 5 minutes) of bedtime. Subjects will also be instructed on study restrictions related to prohibited medications/drugs, caffeine and alcohol, and the prohibitions regarding the use of CPAP device or dental appliance. If SpO₂ <80% for ≥ 20% of TST during the first night of treatment, the subject must be early terminated. Subjects may leave the clinic after the investigator determines that it is safe for them to do so. Subjects will be instructed to promptly contact investigator in case of any new complaints or exacerbation of current symptoms.

On Day 5 (with a window of ±2 days), the site will telephone the subject to assess AEs and record concomitant medications. If any AE is suspected as significant and requires a clinic visit, an Unscheduled Visit should be conducted as soon as possible.

After 6 consecutive nights of administering study drug at home, subjects will return to the clinic and will remain overnight in the sleep laboratory. Subjects will undergo the same procedures as on Day 1 (including urine pregnancy test for female subjects of childbearing potential, a urine drug test, and an breath alcohol test), in addition to which, a blood sample for pre-dose (trough) PK will be taken within 1 hour before dosing. The following morning, a PK blood sample will be collected. Routine safety assessments will also conducted, as indicated in the Schedule of Procedures/Assessments. Subjects will be instructed on study restrictions related to prohibited medications/drugs, alcohol and caffeine, and the prohibitions regarding the use of CPAP device or dental appliance. Subjects may leave the clinic after the investigator determines that it is safe for them to do so.

After Treatment Period 1, there will be a washout interval of at least 14 days.

Treatment Period 2

After the washout interval, subjects will return to the clinic for Treatment Period 2, which will follow the same schedule and procedures as did Treatment Period 1.

When the subject is discharged from the clinic after Treatment Period 2, the Follow-Up Period will begin. The Follow-Up Period will have a duration of at least 14 days, during which the subjects will not receive any treatment.

9.1.2.2.2 FOLLOW-UP PERIOD (OSA COHORT)

At the end of the Follow-Up Period, subjects will return to the clinic for an EOS visit at which safety will be assessed including adverse events, 12-lead ECGs, vital signs, weight, clinical hematology and blood chemistry labs, urine pregnancy test, and suicidality assessed by the C-SSRS. If subjects discontinue prematurely, they will undergo an Early Termination

(ET) Visit and will then be followed for at least 14 days, after which, an EOS visit should be scheduled.

The Treatment Phase assessments and timing thereof are shown in [Section 9.5.1.6.4](#)

9.2 Discussion of Study Design, Including Choice of Control Groups

E2006-A001-102 (Study 102) is a randomized, double-blind, placebo-controlled, crossover study to evaluate the respiratory safety of lemborexant in adult and elderly healthy subjects and adult and elderly subjects with mild obstructive sleep apnea.

9.2.1 Study Design (HV Cohort)

In the HV Cohort, this will be a randomized, double-blind, placebo-controlled, 3-period crossover study.

Eligible healthy adult and elderly subjects will be randomized to treatment sequence A, B or C, each consisting of 3 Treatment Periods, each of one night's duration, in which subjects will receive a single dose of lemborexant 10 mg, or lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 8 evaluable adult subjects (<65 years) and 4 evaluable elderly subjects (≥65 years) complete the study.

Table 1 Study Design (HV Cohort)

Treatment Sequence	Treatment Periods in the HV Cohort		
	1 (one night)	2 (one night)	3 (one night)
A	lemborexant-matched placebo	lemborexant 10 mg	lemborexant 25 mg
B	lemborexant 10 mg	lemborexant 25 mg	lemborexant-matched placebo
C	lemborexant 25 mg	lemborexant-matched placebo	lemborexant 10 mg

9.2.2 Study Design (OSA Cohort)

In the OSA Cohort, this will be a randomized, double-blind, placebo-controlled, 2-period crossover study.

Adult and elderly subjects with mild OSA will be randomized to treatment sequences D or E, each consisting of 2 Treatment Periods, each of 8 nights' duration, in which subjects will receive lemborexant 10 mg or placebo; the Treatment Periods will be separated by a washout

interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 20 evaluable adult subjects (<65 years) and 10 evaluable elderly subjects (≥65 years) complete the study.

Table 2 Study Design (OSA Cohort)

Treatment Sequence	Treatment Periods in OSA Cohort	
	1 (eight nights)	2 (eight nights)
D	lemborexant-matched placebo	lemborexant 10 mg
E	lemborexant 10 mg	lemborexant-matched placebo

9.2.3 Randomization

Randomization will be used in this study to avoid bias in the assignment of subjects to the order of treatment administration, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatments, and to ensure the validity of statistical comparisons across treatments. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.2.3.1 HV Cohort

Subjects who continue to meet the eligibility criteria will be randomized to treatment sequence A, B or C consisting of 3 Treatment Periods, one-night duration each: lemborexant 10 mg, lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. Randomization will be stratified by age (<65 years vs ≥65 years). Subjects will then enter Treatment Period 1.

9.2.3.2 OSA Cohort

Subjects who continue to meet the eligibility criteria will be randomized to treatment sequences D or E consisting of 2 Treatment Periods, 8 nights duration each: lemborexant 10 mg followed by placebo or placebo followed by lemborexant 10 mg, with the treatments periods separated by a washout interval of at least 14 days. Randomization will be stratified by age (<65 years vs ≥65 years). Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio. Subjects will then enter Treatment Period 1.

9.2.4 Adjudication Committee (HV and OSA Cohorts)

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..

9.3 Selection of Study Population

For the HV Cohort, a sufficient number of subjects will be screened in order to ensure that a total of 12 evaluable subjects complete the study ((8 evaluable adult subjects [<65 years] and 4 evaluable elderly subjects [≥ 65 years])). Discontinued subjects may be replaced to ensure 12 subjects complete all 3 Treatment Periods.

For the OSA Cohort, a sufficient number of subjects will be screened in order to ensure that a total of 30 evaluable subjects complete the study (20 evaluable adult subjects [<65 years] and 10 evaluable elderly subjects [≥ 65 years])). Discontinued subjects may be replaced to ensure 20 adults and 10 elderly subjects complete both Treatment Periods.

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 (HV and OSA Cohorts)

Subjects must meet all of the following criteria to be included in this study:

1. Male or female, age ≥ 18 years and ≤ 90 years at the time of informed consent
2. Voluntary agreement and ability to provide written informed consent
3. Reports habitually sleeping for at least 5.5 hours per night
4. Agrees to stay in bed for 7 hours per night for the duration of treatment
5. Reports habitual bedtime between 21:00 and 01:00
6. SpO₂ $\geq 94\%$ assessed as part of vital signs at Screening Visit 1

9.3.2 Additional Inclusion Criteria (HV Cohort)

Subjects must meet the following additional criterion to be included in the HV Cohort:

7. Body mass index (BMI) ≤ 32 kg/m²
8. On Screening PSG (Screening Visit 2) AHI <5

9.3.3 Additional Inclusion Criteria (OSA Cohort)

Subjects must meet the following additional criteria to be included in the OSA Cohort:

9. BMI ≤ 40 kg/m²

10. Obstructive sleep apnea, diagnosed according to the criteria of the International Classification of Sleep Disorders (ICSD), version 3 (ICSD-3)
11. On Screening PSG: AHI ≥ 5 to < 15 (mild severity)

9.3.4 Exclusion Criteria (HV and OSA Cohorts)

Subjects who meet any of the following criteria will be excluded from this study:

1. A current diagnosis of restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorder, or narcolepsy
2. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicate the need for referral for a diagnostic evaluation for the presence of narcolepsy
3. A history of a parasomnia or parasomnia observed on the Screening PSG that in the investigator's opinion makes the subject unsuitable for the study
4. Periodic Limb Movement with Arousal Index (PLMAI) as measured on the Screening PSG:
 - Age 18 to < 65 years: PLMAI ≥ 10
 - Age ≥ 65 years: PLMAI > 15
5. Females who are breastfeeding or pregnant. For females of childbearing potential, the serum beta-human chorionic gonadotropin (β -hCG) pregnancy test must be negative at Visit 1 and the urine pregnancy test must be negative at Screening Visit 2 and Baseline. An additional assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who, within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
 - Total abstinence (if it is their preferred and usual lifestyle)
 - An intrauterine device or intrauterine hormone-releasing system (IUS)
 - A contraceptive implant
 - An oral contraceptive (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

Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

NOTES: 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).

It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, the subject must agree to use a medically acceptable

- method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
6. History of or suspected drug or alcohol use disorder within approximately 2 previous years
 7. A positive urine drug test or breath alcohol test at Screening or Baseline, or unwilling to refrain from use of recreational drugs during the study
 8. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), and unwilling to forego alcohol on the days prior to PSG and to limit alcohol intake to no more than 2 alcohol-containing drinks per day (females) or 3 alcohol-containing drinks per day (males) on all non-PSG days for the duration of his/her participation in the study (NB: alcohol will not be permitted in the sleep laboratory).
 9. Reports habitual caffeine use that is excessive in the opinion of the investigator. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and ≥ 5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation
 10. Known to be human immunodeficiency virus (HIV) positive
 11. Active viral hepatitis (B or C) as demonstrated by positive viral serology at Screening
 12. A prolonged QT/QTc interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated if initial ECG indicates a QTcF interval >450 ms)
 13. Comorbid nocturia resulting in the need to get out of bed to use the bathroom more than 3 times during the night
 14. Any history of medical or psychiatric condition that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
 15. Any suicidal ideation with intent to act with or without a plan, current or within 6 months before the C-SSRS administration during the Screening (e.g. answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS)
 16. Any suicidal behavior (per the Suicidal Behavior section of the C-SSRS) within 10 years of Screening.
 17. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
 18. Used any prohibited prescription or OTC medications within 1 week or 5 half-lives, whichever is longer, before the Screening PSG
 19. Hypersensitivity to lemborexant or excipients
 20. Currently enrolled in another interventional clinical trial or used any investigational drug or device within 30 days or 5 times the half-life, whichever is longer preceding informed consent
 21. Previously participated in other clinical trial of lemborexant

22. Is unable to avoid working a night shift within 2 weeks before the Screening PSG, or between the Screening PSG and EOS
23. Has travelled across 3 or more time zones in the week prior to Screening, or plans to travel across 3 or more time zones during the study
24. Clinically significant findings based on vital signs, physical examination, ECG, or clinical laboratory tests

9.3.5 Additional Exclusion Criteria (HV Cohort)

25. Any valid event of SpO₂ <90% during the Screening PSG
26. Current evidence of a clinically significant, active respiratory disorder. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease, or any other pulmonary disorder identified by review of medical history, physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments.
27. Presence of significant illness (including insomnia) that requires treatment or may influence the study assessments (e.g. psychiatric disorders, disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, cardiovascular system, or a congenital abnormality), malignancy within the past 5 years (other than adequately treated basal cell carcinoma or in situ carcinoma of the cervix), or chronic pain that in the opinion of the investigator could interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.

9.3.6 Additional Exclusion Criteria (OSA Cohort)

28. SpO₂ <80% for ≥ 5% of TST during the Screening PSG
29. Uses or plans to use of CPAP device or dental appliance within 2 weeks of the Screening PSG (Screening Visit 2) or during the study
30. Current evidence of a clinically significant, active respiratory disorder other than OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history, physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments.
31. Current evidence of other clinically significant disease (e.g. psychiatric disorders, disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, cardiovascular system, or a congenital abnormality), malignancy within the past 5 years (other than adequately treated basal cell carcinoma or in situ carcinoma of the cervix), or chronic pain that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. Subjects with insomnia disorder, who complain of difficulties with sleep onset and/or

sleep maintenance, are eligible provided that they meet this criterion. Note that medications to treat insomnia are prohibited; see [Appendix 2](#) of the protocol.

9.4 Treatments

9.4.1 Treatments Administered

HV Cohort

The treatments administered in the HV Cohort will be as follows:

- Lemborexant 10 mg: one 10-mg lemborexant tablet and 2 lemborexant-matched placebo tablets
- Lemborexant 25 mg: two 10-mg lemborexant tablets and one 5-mg lemborexant tablet
- Placebo: 3 lemborexant-matched placebo tablets.

To maintain the blind, additional placebo tablets will be added in order to have a total of 3 tablets administered during each Treatment Period.

Study drug will be administered at bedtime in the clinic (within 5 minutes of lights off) in the evening of Day 1. Treatments will be administered orally with 240 mL (8 fluid ounces) of water.

Table 2 Treatments Administered (HV Cohort)

Treatment Sequence	Treatment Periods in the HV Cohort		
	1 (one night)	2 (one night)	3 (one night)
A	lemborexant-matched placebo	lemborexant 10 mg	lemborexant 25 mg
B	lemborexant 10 mg	lemborexant 25 mg	lemborexant-matched placebo
C	lemborexant 25 mg	lemborexant-matched placebo	lemborexant 10 mg

OSA Cohort

The treatments administered in the OSA Cohort will be as follows:

- Lemborexant 10 mg: one 10-mg lemborexant tablet

- Placebo: one lemborexant-matched placebo tablet.

Study drug will be administered at bedtime in the clinic (within 5 minutes of lights off) in the evening of Days 1 and 8. On Days 2 to 7, subjects will take study drug at home, immediately (within 5 minutes) of the time they intend to try to sleep. Treatments will be administered orally with 240 mL (8 fluid ounces) of water.

Table 3 Treatments Administered (OSA Cohort)

Treatment Sequence	Treatment Periods in OSA Cohort	
	1 (eight nights)	2 (eight nights)
D	lemborexant-matched placebo	lemborexant 10 mg
E	lemborexant 10 mg	lemborexant-matched placebo

9.4.1.1 Identity of Investigational Products

Lemborexant and placebo will be supplied by the sponsor in labeled containers.

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container. The product release certificates for lemborexant and placebo will be included in the clinical study report (CSR) for this protocol.

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study drug will consist of either lemborexant or placebo and will be supplied in a subject medication bottle.

For the HV cohort, the medication bottle for each dose is as follows: lemborexant 10-mg dose consisting of 1 film-coated tablet and 2 lemborexant-matched placebo tablets, lemborexant 25-mg dose consisting of 2 tablets of lemborexant 10 mg and 1 tablet of lemborexant 5 mg, and placebo dose consisting of 3 lemborexant-matched placebo tablets.

For the OSA Cohort, study drug will be provided as lemborexant 10-mg dose consisting of 1 film-coated 10 mg tablet, and placebo dose consisting of 1 lemborexant-matched placebo tablet. For each period, the bottle will contain 9 tablets (8 tablets and 1 tablet as overage).

9.4.1.2 Chemical Name, Structural Formula of lemborexant

- Test drug code: E2006
- Generic name: lemborexant

- 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: 410.42

9.4.2 Comparator Drug

Not applicable

9.4.2.1 Labeling for Study Drug

Lemborexant will be labeled in accordance with text that is in full regulatory compliance with regulations in the United States.

9.4.2.2 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 Sequences

Subjects will be assigned to treatments (or treatment sequences) based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.4.4 Selection of Doses in the Study

In the HV cohort (single dose study), lemborexant 10 mg and lemborexant 25 mg have been selected. The single dose of lemborexant 25 mg would correspond to the levels of C_{max} and AUC achieved at the steady state after multiple doses of lemborexant 10 mg.

In the OSA cohort, the lemborexant dose of 10 mg was chosen as the maximum dose being studied in the insomnia Phase 3 program.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will remain overnight in the sleep laboratory. Bedtime (lights off) will be at the median bedtime (MHB) that was used at the second Screening Visit (Visit 2). Subjects will receive study drug immediately (within 5 minutes) before lights off.

9.4.6 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in [Section 9.5.4.5](#). If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. The investigator is to record the date and time and the reason for breaking the code.

9.4.7 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent or 90 days before first dose/administration of study drug, if appropriate) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any adverse event (AE) for which the concomitant medication/therapy was administered.

OSA subjects will be required to abstain from using a CPAP device or dental appliance for at least 2 weeks before the Screening PSG, and throughout the study (until after the EOS Visit).

Subjects must abstain from the use of recreational drugs throughout the study. No alcohol will be permitted in the clinic.

Prohibited medications ([Appendix 2](#) of the protocol)] should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before Screening Visit 2.

Prohibited medications include strong CYP3A inhibitors and all CYP3A inducers as listed in [Appendix 2](#). Prohibited medications also include any pharmacological treatment for insomnia disorder, including any medications (hypnotics or medications with known sedating

effects) that are used for the purpose of inducing sleep or for treating OSA. These prohibitions apply even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not specified as prohibited but is in the same class as a medication that is listed in [Appendix 2](#) of the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

If a subject starts any prohibited medication or therapy, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study as listed in [Appendix 2](#).

9.4.8 Prohibitions and Restrictions during Study Period

9.4.8.1 Food and Water

Not applicable.

9.4.8.2 Beverage and Other Restrictions

Subjects must forego alcohol on day of PSG and to limit alcohol intake to no more than 2 alcohol-containing drinks per day (females) or 3 alcohol-containing drinks per day (males) on all non-PSG days for the duration of his/her participation in the study. Alcohol will not be permitted in the sleep laboratory. Caffeine will be permitted in limited quantities during the study. Subjects will be advised to limit caffeine consumption to ≤ 4 cups of caffeinated beverages per day, or ≤ 400 mg caffeine per day. They will be instructed to avoid caffeine after 13:00 on days when they are scheduled for a PSG recording and after 18:00 on all other days during the study. Subjects must forego grapefruit juice during the duration of the study.

9.4.8.3 Physical Activity Restrictions

Not applicable.

9.4.9 Treatment Compliance

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 (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 to be used other than as directed by this protocol. Study drugs 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, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs 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 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, Medicine and Healthcare products Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be

returned to the investigator by the subject and together with unused study drugs 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 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 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 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 may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs 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 will include date of birth, sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

Baseline assessments shall include inclusion/exclusion criteria, medical history, sleep diary, safety assessments ([Section 9.5.1.5](#)), PSG (with Pulse Oximetry), and C-SSRS.

9.5.1.2.1 MEDICAL HISTORY

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

9.5.1.2.2 SLEEP DIARY

The Sleep Diary will be completed within an hour of morning waketime on each morning of the Screening Period until the Screening PSG. This Sleep Diary will yield information on the MHB that will be used to determine eligibility, and to determine bedtime (lights off) in the clinic.

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

A single blood (4 mL) sample for plasma concentrations of lemborexant and its metabolites M4, M9 and M10 will be taken at predefined visits (see [Schedule of Procedures/Assessments](#)). The time and date of the 2 most recent doses administered before each sample will be documented. PK sample collection, processing, handling and shipping instructions will be provided either as a stand-alone PK lab manual or as part of the central labs manual.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

PSG

Each PSG recording will include an electrode montage with electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), and ECG channels. In addition, the montage will include channels for recording respiratory variables including pulse oximetry. In addition, the Screening PSG will include channels for assessment of symptoms of periodic limb movement disorder.

Trained PSG scorers will score PSG records in 30-second epochs according to standard criteria. At Screening Visit 2, the PSG will be used to calculate AHI and PLMAI for evaluation of eligibility criteria. Subsequent PSGs will be used to determine:

- AHI: the number of apneas and hypopneas divided by the TST (in minutes) and multiplied by 60 (min / hour) (ie, the average number of apneas and hypopneas per hour of sleep), as defined by the American Academy of Sleep Medicine (respiratory safety/PD assessment)
- SpO₂ level

Transmissive pulse oximetry is a noninvasive method for monitoring peripheral oxygen saturation (SpO₂). A sensor device is placed on a thin part of the subject's body; in the present study, this will be a fingertip. The device passes two wavelengths of light through the body part to a photodetector. This measures the changing absorbance at each of the wavelengths, allowing determination of the absorbance caused by the pulsing arterial blood alone, excluding venous blood, skin, bone, muscle and fat. The reading of oxygen saturation by pulse oximetry is not necessarily identical to the reading of arterial oxygen saturation (SaO₂) from (invasive) analysis of arterial blood gas, but the two are sufficiently correlated that pulse oximetry is valuable for measuring oxygen saturation in a clinical setting, including in clinical trials.

Further details are provided in PSG manual.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in [Table 5](#) and [Table 6](#). Safety will be assessed at every clinic visit throughout the study, including after the last dose of study drug, and at the EOS Visit.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An adverse event (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(s) 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 nonprotocol-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. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious AEs will be collected for 28 days after the last dose

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.

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see [Section 9.5.1.5.7](#) for a description of the C-SSRS).

All AEs must be followed for 28 days 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 adverse event 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 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5 and Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 List of Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium, calcium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Total protein, albumin, globulin, cholesterol, triglycerides, glucose, lactate dehydrogenase, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

CYP3A = cytochrome P450 Family 3A, RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by PPD Clinical Laboratories. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples may be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central

laboratory: A central laboratory will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

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], and peripheral oxygen saturation (SpO₂) [percentage]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting 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

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)). 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.

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. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narratives for the event, per [Section 9.2.4](#), Adjudication Committee.

9.5.1.5.6 ELECTROCARDIOGRAMS

Twelve-lead electrocardiograms will be obtained and reviewed locally as designated in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)).

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 OTHER SAFETY ASSESSMENTS

Columbia-Suicide Severity Rating Scale (C-SSRS)

An assessment of suicidal ideation, suicidal thoughts and self-injurious behavior using the C-SSRS ([Posner et al., 2011](#)) will be performed at Screening, Baseline, and at the Follow-Up Visit, as designated in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)).

Qualified personnel must evaluate responses on the C-SSRS and take appropriate action as detailed in the training and certification process for administering the C-SSRS.

9.5.1.6 Other Assessments

9.5.1.6.1 VIRAL TESTS

A 6 mL sample of blood will be taken for hepatitis B surface antigen and hepatitis C antibodies at Screening.

9.5.1.6.2 PREGNANCY TEST

A serum β -hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. Urine pregnancy tests will be performed for all subsequent visits. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)).

9.5.1.6.3 URINE DRUG TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)). This sample will be tested for common drugs of use/abuse: eg, cocaine, cannabinoids, PCP, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.1.6.4 BREATH ALCOHOL TEST

A breath alcohol test will be obtained at designated time points as specified in the Schedule of Procedures/Assessments ([Table 5](#) and [Table 6](#)).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedules of Procedures and Assessments for the HV and OSA Cohorts

HV Cohort

[Table 5](#) presents the schedule of procedures/assessments for the HV cohort of this study.

Table 5 Schedule of Assessments and Procedures for the HV Cohort in Study E2006-A001-102

Phase	Prerandomization				Randomization						UN ^b
	Screening			BL	Treatment 1	Treatment 2		Treatment 3		Follow-Up	
Period	1	2A	2B	3A	3B	4A	4B	5A	5B	6 EOS/ET ^a	
Visit											
Study Day	-21 to -8	-15 to -2	-14 to -1	1	2 ^d	16 ^c	17 ^d	31 ^c	32 ^d	46 ^{c,e}	
Demography	X										
Informed consent	X										
Inclusion/exclusion criteria	X	X		X							
Medical, psychiatric, and sleep history ^f	X										
Physical examination	X			X						X	X
Viral serology	X										
Sleep diary ^g	----->										
Urine drug test ^h	X	X		X		X		X			X
Breath alcohol test	X	X		X		X		X			X
Height	X										
Weight	X									X	X
Clinical laboratory tests ⁱ	X			X						X	X
PK blood sampling ^j					X	X	X	X	X		
Pregnancy test ^k	X			X		X		X		X	X
Vital signs ^l	X	X		X	X	X	X	X	X	X	X

Table 5 Schedule of Assessments and Procedures for the HV Cohort in Study E2006-A001-102

Phase	Prerandomization				Randomization						UN ^b
	Screening			BL	Treatment 1	Treatment 2		Treatment 3		Follow-Up	
Period	1	2A	2B	3A	3B	4A	4B	5A	5B	6 EOS/ET ^a	
Visit											
Study Day	-21 to -8	-15 to -2	-14 to -1	1	2 ^d	16 ^c	17 ^d	31 ^c	32 ^d	46 ^{c,e}	
12-lead ECG	X			X						X	X
Randomization				X							
Administer study drug in clinic ^m				X ^l		X		X			
PSG (with Pulse Oximetry) ⁿ		X ⁿ		X ^l		X		X			
C-SSRS	X			X						X	
+7-day window						X		X		X	
Adverse events ^o	----- →										
Prior and concomitant medications	----- →										
Admit to clinic		X		X		X		X			
Discharge from clinic			X		X		X		X		
Discharge from study										X	

BL = baseline; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; PK = pharmacokinetic; OSA = obstructive sleep apnea PLMD = periodic limb movement disorder; PSG = polysomnography; UN = Unscheduled Visit.

- a: Assessments as shown will be conducted at EOS visit and for subjects who discontinue the study early after Visit 3.
- b: The assessments at an Unscheduled Visit will be conducted at the Investigator’s discretion.
- c: Within a +7-day window period.

- d: Visit must be followed by a washout interval of 14 days to 21 days in duration.
- e: EOS visit is 14 days to 21 days after the final study dose. Subjects who undergo an ET will be followed for at least 14 days, after which, an EOS visit should be scheduled.
- f: Sleep history will include: history of obstructive sleep apnea (OSA), including treatments used for OSA, history of falls, history of periodic limb movement disorder (PLMD), restless leg syndrome, circadian rhythm disorder and narcolepsy.
- g: Sleep diary should be completed by the subjects within 1 hour of waketime on 5 consecutive mornings during Screening, before Screening Visit 2. Sleep diaries should be reviewed for eligibility before or during check-in at Screening Visit 2. The median habitual bedtime (MHB) calculated from the Sleep Diary during Screening will be used to schedule subjects' PSG recordings on each night spent in the clinic. Sleep diaries will be completed on a paper form.
- h: Urine drug test will be conducted using a dipstick.
- i: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
- j: One blood sample (approximately 4 mL) for determination of plasma concentrations of lemborexant and metabolites M4, M9, and M10 will be obtained at the following time points: within 1 hour predose in the clinic (Treatment Periods 2 and 3) and within 1 hour of waking after each PSG recording (Treatment Periods 1, 2, and 3). The time of each PK blood draw must be recorded.
- k: Only for female subjects of childbearing potential. A serum pregnancy test will be performed at Screening Visit 1 and a urine pregnancy test at all other specified time points.
- l: Vital signs include systolic and diastolic blood pressure, heart rate, and respiratory rate. Oxygen saturation as measured by a pulse oximeter will be recorded at Screening Visit 1 only.
- m: At Visit 3A, administered after all baseline assessments have been completed.
- n: PSG will include channels for assessment of symptoms of periodic limb movement disorder at Screening Visit 2A only.
- o: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per [Section 9.2.4](#) Adjudication Committee.

OSA Cohort

Table 6 presents the schedule of procedures/assessments for OSA cohort of the study.

Table 6 Schedule of Procedures and Assessments for OSA Cohort in Study E2006-A001-102

Phase	Prerandomization				Randomization									UN ^c	
	Screening			BL	Treatment 1			Treatment 2			Follow-Up				
Period	1	2A	2B	3A	3B	4 ^a	5A	5B	6A	6B	7 ^a	8A	8B	9 EOS/ET ^b	
Visit	1	2A	2B	3A	3B	4 ^a	5A	5B	6A	6B	7 ^a	8A	8B	9 EOS/ET ^b	
Study Day	-21 to -8	-15 to -2	-14 to -1	1	2	5	8	9 ^d	23 ^e	24	27	30	31	45 ^{e,f}	
Demography	X														
Informed consent	X														
Inclusion/exclusion criteria	X	X		X											
Medical, psychiatric, and sleep history ^g	X														
Physical examination	X			X										X	X
Viral serology	X														
Sleep diary ^h	----->														
Urine drug test ⁱ	X	X		X			X		X			X			X
Breath alcohol test	X	X		X			X		X			X			X
Height	X														
Weight	X													X	X
Clinical laboratory tests ^j	X			X										X	X
PK blood sampling ^k					X		X	X	X	X		X	X		
Pregnancy test ^l	X			X			X		X			X		X	X
Vital signs ^m	X	X		X	X		X	X	X	X		X	X	X	X
12-lead ECG	X			X										X	X

Table 6 Schedule of Procedures and Assessments for OSA Cohort in Study E2006-A001-102

Phase	Prerandomization				Randomization										UN ^c
	Screening			BL	Treatment 1				Treatment 2				Follow-Up		
Period	1	2A	2B	3A	3B	4 ^a	5A	5B	6A	6B	7 ^a	8A	8B	9 EOS/ET ^b	
Visit	1	2A	2B	3A	3B	4 ^a	5A	5B	6A	6B	7 ^a	8A	8B	9 EOS/ET ^b	
Study Day	-21 to -8	-15 to -2	-14 to -1	1	2	5	8	9 ^d	23 ^e	24	27	30	31	45 ^{e,f}	
Randomization				X											
Administer study drug in clinic ⁿ				X ⁿ			X		X			X			
Study drug taken at home						----->				----->					
PSG (with Pulse Oximetry) ^o		X ^o		X			X		X			X			
C-SSRS	X			X										X	
+7-day window									X					X	
±2-day window						X					X				
Adverse events ^p	----->														
Prior and concomitant medications	----->														
Admit to clinic		X		X			X		X			X			
Discharge from clinic			X		X			X		X			X		
Discharge from study														X	

AHI = apnea-hypopnea index; BL = baseline; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; PK = pharmacokinetic; OSA = obstructive sleep apnea PLMD = periodic limb movement disorder; PSG = polysomnography; UN = Unscheduled Visit.

a: Telephone visits.

b: Assessments as shown will be conducted at the EOS visit and for subjects who discontinue the study early after Visit 3.

- c: The assessments at an Unscheduled Visit will be conducted at the Investigator's discretion.
- d: Visit must be followed by a washout interval of 14 to 21 days in duration.
- e: Within a + 7-day window period.
- f: EOS visit is 14 days to 21 days after the final study dose. Subjects who undergo an ET will be followed for at least 14 days, after which, an EOS visit should be scheduled.
- g: Sleep history will include: history of obstructive sleep apnea (OSA), including treatments used for OSA, history of falls, history of periodic limb movement disorder (PLMD), restless leg syndrome, circadian rhythm disorder and narcolepsy.
- h: Sleep diary should be completed by the subjects within 1 hour of waketime on 5 consecutive mornings during Screening, before Screening Visit 2. Sleep diaries should be reviewed for eligibility before or during check-in at Screening Visit 2. The median habitual bedtime (MHB) calculated from the Sleep Diary during Screening will be used to schedule subjects' PSG recordings on each night spent in the clinic.
- i: Urine drug test will be conducted using a dipstick.
- j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
- k: One blood sample (approximately 4 mL) for determination of plasma concentrations of lemborexant and metabolites M4, M9, and M10 will be obtained at the following time points: within 1 hour predose in the clinic (before the second PSG of Treatment Period 1 and Treatment Period 2) and within 1 hour of waking after each PSG recording (Treatment Periods 1 and 2). The time of each PK blood draw must be recorded.
- l: Only for female subjects of childbearing potential. A serum pregnancy test will be performed at Screening Visit 1 and urine pregnancy test at all other specified time points.
- m: Vital signs include systolic and diastolic blood pressure, heart rate, and respiratory rate. Oxygen saturation as measured by a pulse oximeter will be recorded at Screening Visit 1 only.
- n: At Visit 3A, administered after all baseline assessments have been completed.
- o: Screening PSG will include channels for assessment of symptoms of periodic limb movement disorder (PLMD).
- p: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per [Section 9.2.4](#) Adjudication Committee.

9.5.2.2 Description of Procedures/Assessments Schedule

9.5.2.3 Total Volume of Blood Sampling

HV COHORT

Table 7 presents the number of blood samples and the total volume of blood that will be collected throughout the study for the HV Cohort. 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 7 Summary of Blood Sample Volumes (HV Cohort)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Follow-Up: 1	12×2=24
Viral test	6	Screening: 1	6×1=6
PK blood sampling	4	5	4×5=20
Total			50

OSA COHORT

Table 8 present the number of blood samples and the total volume of blood that will be collected throughout the study for the OSA Cohort. 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 8 Summary of Blood Sample Volumes (OSA Cohort)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Follow-Up: 1	12×2=24
Viral test	6	Screening: 1	6×1=6
PK blood sampling	4	7	4×7=28
Total			58

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of respiratory safety and in particular, Mild Obstructive Sleep Apnea.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, ECG, 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.

Serious adverse events, regardless of causality assessment, must be collected through the last visit 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. 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 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 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

Adverse events 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.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Not applicable.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators 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

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events 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 the 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 5](#) and [Table 6](#)).

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 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 will be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per [Section 9.5.1.5.1](#). Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

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.

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 by the sponsor or designee after the study is completed and the database is locked and released for unblinding. 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 and treatment unblinding.

9.7.1.1 Study Endpoints

Details of statistical methods and analyses will be specified in the SAP.

The following analyses will be performed on the PD Analysis Set for each cohort:

9.7.1.1.1 PRIMARY ENDPOINT (HV COHORT)

The mean SpO₂ during TST on Day 1 of treatment.

9.7.1.1.2 SECONDARY ENDPOINTS (HV COHORT)

1. The AHI on Day 1 of treatment.
2. The percentage of TST during which SpO₂ is <90%, <85% and <80% on Day 1 of treatment
3. The proportion of subjects with at least one incident of SpO₂ <90% for at least 30 seconds during TST on Day 1 of treatment

9.7.1.1.3 PRIMARY ENDPOINT (OSA COHORT)

The AHI on Day 8 of treatment.

9.7.1.1.4 SECONDARY ENDPOINTS (OSA COHORT)

1. The AHI on Day 1 of treatment
2. The mean SpO₂ during TST on Day 1 and Day 8 of treatment
3. The proportion percentage of TST during which the SpO₂ is <90%, <85% and <80% on Day 1 and Day 8 of treatment
4. The proportion of subjects with at least one incident of SpO₂ <90% for at least 30 seconds during TST on Day 1 and Day 8 of treatment.

9.7.1.1.5 EXPLORATORY ENDPOINTS (HV AND OSA COHORTS)

1. The mean SpO₂ during REM sleep, NREM and wake
2. The AHI during REM and NREM sleep
3. The AHI separately for adult and elderly subjects at all days assessed
4. The mean SpO₂ during TST separately for adult and elderly subjects at all days assessed

9.7.1.1.6 PHARMACOKINETIC ENDPOINT (HV AND OSA COHORTS)

Lemborexant and metabolites M4, M9 and M10 plasma concentrations

9.7.1.1.7 PHARMACOKINETIC/PHARMACODYNAMIC (EXPOSURE-RESPONSE) ENDPOINT (HV AND OSA COHORTS)

Correlations between plasma concentrations of lemborexant and select safety variables including AHI, mean SpO₂ during TST, and proportion of TST in which SpO₂ is <90%, <85% and <80% at all days assessed.

9.7.1.2 Definitions of Analysis Sets

Safety Analysis Set: Group of subjects who received study drug and have at least one postdose safety assessment.

Pharmacodynamic Analysis Set: The PD Analysis Set is the group of subjects who received at least 1 dose of study drug in each Treatment Period and who had sufficient PD data to derive at least 1 primary PD parameter.

Pharmacokinetic Analysis Set: Group of subjects who received at least 1 dose of lemborexant and who had sufficient PK data to derive at least 1 PK parameter.

9.7.1.3 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects randomized along with the number of subjects in each of the study populations will also be presented.

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Other reasons for study drug and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each sequence and overall using descriptive statistics. Continuous demographic and baseline variables include age height, and weight; BMI; categorical variables include sex, age group (<65, 65 to 74 years, 75 to 84 years, and 85 and older), BMI group, race, and ethnicity.

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) (Mar 2016 or latest version). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. All medications will be presented in subject data listings.

Prior medications are defined as medications that stopped before the first dose of study drug, where study drug includes placebo.

Concomitant medications are defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug to the last dose day plus 14 days. 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 lemborexant and M4, M9 and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and M4, M9 and M10 plasma concentrations.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic Analyses

The following analysis will be performed on the PD Analysis Set for each cohort.

Analysis for the Primary Endpoint

HV Cohort: Mean SpO₂ during TST will be analyzed using a mixed effect model. The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: LS means, difference in LS mean of lemborexant 10 mg and lemborexant 25 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided lower 95% CI) for the true mean difference (lemborexant – placebo) in SpO₂ and *p*-value. If the lower bound of the one-sided 95% CI of the treatment difference of SpO₂ is less than -5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO₂ compared to placebo.

OSA Cohort: AHI will be analyzed using a mixed effect model., The model will include fixed effects for, sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: LS means, difference in LS mean of lemborexant 10 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided upper 95% CI) for the true mean difference (lemborexant – placebo) in AHI and *p*-value. If the upper bound of the one-sided 95% CI of the treatment difference of AHI is less than 5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant increase in AHI with mild OSA compared with placebo.

A sensitivity analysis may also be performed on the primary endpoint where outliers are excluded. Other sensitivity analyses may be explored.

Plots of AHI and SpO₂ treatment difference data (both individual and LS Mean) will be used to explore the results.

Analysis for the Secondary Endpoints

The continuous secondary endpoints will be analyzed using the same model as the primary endpoint. Treatment comparison will be performed using contrasts.

The proportion of subjects with SpO₂ <90% will be summarized using descriptive statistics. All analyses will be performed separately for each cohort.

Analysis for the Exploratory Endpoints

Summaries and plots of all endpoints may be produced for appropriate subgroups (eg, age group, sex, BMI, race).

Subgroup analyses will also be performed as appropriate on primary and all secondary endpoints. All analyses will be performed separately for each cohort.

Pharmacokinetic/Pharmacodynamic (Exposure-Response) Analyses

The exposure-response (E-R) relationship between plasma concentrations of lemborexant after PSG, and selected PD parameters including but not limited to the respiratory safety variables (including AHI, mean SpO₂ during TST, and proportion of TST in which SpO₂ is <90%, <85% and <80% will be explored graphically. Any emergent relationship may be followed using population model-based analysis. The potential effect of covariates (eg, age) on the E-R relationship may be tested. The PK Analysis Set will be used for these assessments. All analyses will be performed separately for each cohort.

Pharmacodynamic, PG, and other biomarker analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, where presented by treatment, will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include the incidence of AEs, treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and suicidality variables (C-SSRS). All analyses will be performed separately for each cohort.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of subjects exposed to each treatment will be summarized descriptively by treatment, and a listing will also be provided.

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 MedDRA. Adverse events 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 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 treatment. 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]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by cohort/dose level and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by system organ class (SOC) and by preferred term (PT) will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

Adverse events will be summarized by the following subgroups: age, sex (male, female), and race (white, black, Asian, and other) if there are sufficient numbers in a category.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each treatment. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment. A subject data listing of all AEs leading to discontinuation from study drug 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 treatment 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-treatment 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. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

[Appendix 1](#) (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 OTHER SAFETY ANALYSES

Not applicable.

9.7.1.9 Other Analyses

Not applicable

9.7.2 Determination of Sample Size

HV Cohort

A mean difference of 5 percentage points between treatments in SpO₂ is considered to be clinically meaningful in a study of the respiratory safety of suvorexant in healthy adult

volunteers (Uemura, et al., 2015). From that source, the within-subject variance is assumed to be 0.315%. With a total of 12 subjects (4 elderly and 8 adults) completing the study and assuming that the true difference between treatments is -1.0, there is 99% power that the lower bound of the 90% confidence interval for the difference in SpO₂ (lemborexant - placebo) would be greater than -5. Although the estimate of within-subject variability is based on a study of adult healthy volunteers, the addition of elderly subjects is expected to have a minimal effect on the combined variability and thus a minimal effect on the power.

OSA Cohort

A mean difference between treatments in AHI > 5 is considered clinically meaningful in studies of the respiratory safety of sleep agents in OSA (Kryger, et al., 2007, Sun, et al., 2016). The within-subject variance is assumed to be 25.34 for AHI for adult subjects (Sun, et al, 2016) and 30.41 for AHI for elderly subjects (where the elderly within-subject variance is estimated from adult data + 20% (Mitterling, et al, 2015; Lee, et al., 2016). Assuming the true difference in AHI (lemborexant – placebo) on Day 8 is as high as 1.5, a total of 30 subjects completing the study (20 adult, 10 elderly), provides 82% power that the upper bound of the 90% CI for the treatment difference in AHI (lemborexant – placebo) on Day 8 would be < 5.

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.

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C-SSRS Reference

http://www.cssrs.columbia.edu/scales_cssrs.html

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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 submission to regulatory authorities as well as additional approval by the applicable IRBs. 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/or study director and the IRB 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, but the health or regulatory authority and IRB 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 and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

The 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

11.4 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 correction 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.

11.5 Identification of Source Data

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

11.6 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 correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. 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.

11.7 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.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. 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 drug packaging vendor for drug destruction. A copy of the completed drug disposition form will be forwarded to the sponsor.

11.9 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 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, as appropriate.

11.10 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/ 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.

11.11 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 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 and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 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 – 2.0×10 ⁹ /L <3000 – 2000/mm ³	<2.0 – 1.0×10 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 – 0.5×10 ⁹ /L	<500 – 200/mm ³ <0.5 – 0.2×10 ⁹ /L	<200/mm ³ <0.2×10 ⁹ /L
Neutrophils	<LLN – 1.5×10 ⁹ /L <LLN – 1500/mm ³	<1.5 – 1.0×10 ⁹ /L <1500 – 1000/mm ³	<1.0 – 0.5×10 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 – 50.0×10 ⁹ /L <75,000 – 50,000/mm ³	<50.0 – 25.0×10 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 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	<ul style="list-style-type: none"> • Barbiturates • Benzodiazepines • GABA analogues • Hydantoins • Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter)	<ul style="list-style-type: none"> • Diphenhydramine • Carbinoxamine • Doxylamine • Dimenhydrinate • Triprolidine • Brompheniramine • Chlorphenamine • Hydroxazine
Antihistamines with known sedating effects	<i>Non-sedating, eg, Loratidine is not prohibited</i>
Anxiolytics with known sedating effects	<ul style="list-style-type: none"> • Lorazepam • Alprazolam • Buspirone

Category	Medication
Strong CYP3A inhibitors	<ul style="list-style-type: none"> • Amiodarone • Cimetidine • Clarithromycin • Diltiazem • Erythromycin • Fluvoxamine • Grapefruit juice • Itraconazole • Ketoconazole • Mibefradil • Nefazodone • Troleandomycin • Verapamil
CYP3A inducers	<ul style="list-style-type: none"> • Carbamazepine • St. John's Wort • Phenobarbital • Troglitazone • Phenytoin • Rifabutin • Rifampin
Hypnotics	Melatonin(prescribed or OTC)
Herbal preparations with sedating effects	-
MAOIs	-
Opioid Analgesics	-
Muscle relaxants (centrally-acting) with known sedating effects	<ul style="list-style-type: none"> • GABA analogues • Hydantoins • Phenyltriazines
Stimulants	<ul style="list-style-type: none"> • Amphetamines • Modafinil • Armodafinil • Methylfenidate • Theophylline
Other	<ul style="list-style-type: none"> • Warfarin, heparin, ticlopidine

Category	Medication
	<ul style="list-style-type: none">• Non-stimulant diet pills• Systemic isotretinoin• Systemic glucocorticoids• Tryptophan

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-102

Study Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Healthy Subjects and Adult and Elderly Subjects with Mild Obstructive Sleep Apnea

Investigational Product Name: E2006/Lemborexant

SIGNATURES	
Authors:	
<hr/> <p>PPD [Redacted] PPD [Redacted] [Redacted] Neuroscience Business Group Eisai Inc.</p>	Date
<hr/> <p>PPD [Redacted] PPD [Redacted] [Redacted] Neuroscience Business Group Eisai Inc.</p>	Date
<hr/> <p>PPD [Redacted] PPD [Redacted] [Redacted] Eisai Inc.</p>	Date
<hr/> <p>PPD [Redacted] PPD [Redacted] [Redacted] Eisai Inc.</p>	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: E2006-A001-102

Study Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Healthy Subjects and Adult and Elderly Subjects with Mild Obstructive Sleep Apnea

Investigational Product Name: E2006/Lemborexant

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 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