REVISION HISTORY

Revisions to Version 1.0

New version/date: Version 2.0/13 Jul 2020 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Revised treatments in Treatment Period 2 for appropriate representation of crossover design and included footnotes to maintain consistency with the schedule of assessment table, Figure 1	To clarify that patients will crossover to the alternative treatment	Figure 1
Revised the duration of study period from 5 to 9 months	Correction	Section 2 Synopsis-Study Period and Phase of Development
Deleted footnote citation "n" for polysomnography (PSG) from Visit 2A in the schedule of assessment table Deleted footnote citation "n" in the rows for "Administer study drug in clinic" in the schedule of assessment table	To clarify that the PSG is performed during the Screening period for both obstructive sleep apnea (OSA) and obstructive pulmonary disease (COPD) cohorts To correct erroneously placed superscript	Table 4
Added footnotes "q" and "r" to PSG for Baseline Period 1 and Baseline Period 2, respectively, in the schedule of assessment table	To clarify that PSG will occur after randomization and study drug administration during Baseline period 1, and after study drug administration during Baseline Period 2	Table 4
Marked 'inclusion/exclusion' criteria and oxygen saturation assessments for Baseline Period 2	To clarify that inclusion/exclusion criteria will be reevaluated during Baseline Period 2	Section 2 Synopsis-Study Design Table 4 Section 9.1.2
Mentioned that the oxygen saturation as measured by a pulse oximeter will also be recorded at Visit 3A and Visit 6A in addition to Visit 1	To confirm that the subject continues to meet oxygen saturation criteria requirements	Table 4
Exclusion criterion added to chronic obstructive pulmonary disease (COPD) cohort as follows: recent changes to COPD medications or recent acute exacerbation of COPD (ie, needing hospitalization or treatment with oral corticosteroids and/or antibiotics) within 3 months of enrollment	To clarify that COPD patients should be on a stable COPD treatment regimen and have stable disease prior to study enrollment	Section 2 Synopsis-Exclusion Criteria (COPD Cohort) Section 9.3.2

Revisions to Version 1.0

New version/date: Version 2.0/13 Jul 2020 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Exclusion criteria added to obstructive sleep apnea (OSA) and COPD cohorts as follows: Exposure within the last 14 days to an individual with confirmed or probable corona virus disease 2019 (COVID-19) or symptoms within the last 14 days that are on the most recent Centers for Disease Control and Prevention (CDC) list of COVID symptoms or any other reason to consider the subject at potential risk for an acute COVID-19 infection	To avoid potential risk of COVID-19	Section 2 Synopsis-Additional Exclusion Criteria (OSA and COPD Cohorts) Section 9.3.2
Added oxygen desaturation index (ODI) and absolute number of desaturations (with desaturation defined as a ≥3% reduction from baseline peripheral capillary oxygen saturation [SpO2]) to secondary objectives and endpoints, and pharmacodynamic (PD) assessments	To further assess secondary measures of respiratory safety per FDA recommendation	Section 2 Synopsis-Secondary Objectives Section 2 Synopsis-Statistical Methods Section 2 Synopsis-Assessments Section 8.2 Section 9.5.1.3.2 Section 9.7.1.1.2 Section 9.7.1.1.4
Deleted sensitivity analysis	Correction	Section 2 Synopsis-Pharmacodynamic analyses Section 9.7.1.7.2
Revised description of primary endpoint for OSA and COPD Cohorts to state that the mean apnea hypopnea index (AHI) will be analyzed on the PD analysis set	To clarify what population will be used for the primary analysis	Section 2 Synopsis-Statistical methods Section 9.7.1.7.2
Mentioned that further details of the analysis will be provided in the statistical analysis plan (SAP)	To align estimands with the clinical objective for each cohort	Section 2 Synopsis-Statistical methods Section 9.7.1.7.2

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2006-A001-113
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Subjects With Moderate to Severe Obstructive Sleep Apnea and Adult and Elderly Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677, US
Investigational Product Name:	E2006/lemborexant
Indication:	Not applicable
Approval Date:	V1.0 06 Apr 2020 (original protocol) V2.0 13 Jul 2020 (Amendment 01)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of 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 Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Subjects With Moderate to Severe Obstructive Sleep Apnea and Adult and Elderly Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease

Sites

Approximately 10 sites in the US

Study Period and Phase of Development

First Subject Screened to Last Subject Out: Approximately 9 months (revised per Amendment 01).

Phase 1

Objectives

Obstructive Sleep Apnea Cohort:

Primary Objective

- Using polysomnography (PSG), determine whether lemborexant increases the apnea hypopnea index (AHI) on Day 8 of treatment in adult and elderly subjects (adults ≥45 to <65 years; elderly ≥65 to 90 years) with moderate to severe obstructive sleep apnea (OSA) compared with placebo

Secondary Objectives

- Using PSG, determine whether lemborexant increases the AHI on Day 1 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the mean oxygen saturation (SpO2) during total sleep time (TST) on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the peripheral capillary oxygen saturation (SpO2) is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the mean oxygen desaturation index (ODI) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Using pulse oximetry, determine whether lemborexant increases the absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Evaluate safety and tolerability of lemborexant compared with placebo

Chronic Obstructive Pulmonary Disease Cohort:

Primary Objective

- Using pulse oximetry, determine whether lemborexant decreases mean SpO2 during TST on Day 8 of treatment in adult and elderly subjects (adults ≥45 to <65 years; elderly ≥65 to

90 years) with moderate to severe chronic obstructive pulmonary disease (COPD) compared with placebo

Secondary Objectives

- Using pulse oximetry, determine whether lemborexant decreases mean SpO2 during TST on Day 1 of treatment compared with placebo
- Using PSG, determine whether lemborexant increases the AHI on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the SpO2 is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the mean ODI on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Using pulse oximetry, determine whether lemborexant increases the absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Evaluate safety and tolerability of lemborexant compared with placebo

OSA and COPD Cohorts:

Exploratory Objectives

Explore the effects of lemborexant compared with placebo on the following for Days 1 and 8 of treatment:

- The mean SpO2 during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
- AHI during REM and NREM sleep
- Determine whether lemborexant increases the AHI, and decreases the mean SpO2 during TST separately for adult and elderly subjects
- Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10)
- Explore the effect of lemborexant on blood biomarkers potentially related to dementia, OSA and/or COPD

Study Design

In both the OSA and COPD Cohorts, this will be a randomized, double-blind, placebo-controlled, 2-period crossover study. 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. In the Randomization Phase subjects will be randomized in treatment sequences A or B (OSA Cohort), or treatment sequences C or D (COPD Cohort) consisting of 2 Treatment Periods, each of 8 days duration, separated by a washout interval of at least 14 days, and a Follow-up Period of approximately 28 days. Approximately 28 days after the final study dose, there will be an end of study (EOS) Visit.

Prerandomization Phase:

Screening Period

The Screening Period will begin no more than 21 days before the subject is randomized and during which 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. Subjects eligible for the COPD Cohort will then undergo screening spirometry between Visit 1 and Visit 2 (designated Visit 1A),

which may be performed at the study site, or offsite, so long as a final report is available for review at the study site by Visit 2. Spirometry will be performed based on Global Initiative for Obstructive Lung Disease (GOLD) recommendations.

After at least 6 days of the initial Screening visit, (to allow subjects the opportunity to complete the sleep diary for at least 5 nights), subjects will return to the clinic for the second Screening Visit to undergo PSG. For subjects being evaluated for the COPD Cohort, results of screening spirometry will also be reviewed.

Subjects who continue to meet the eligibility criteria will remain overnight in the sleep laboratory. The mean 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 severity (only mild for the OSA Cohort, and moderate to severe for the COPD Cohort), 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 Baseline Period.

Baseline Period

At the Baseline Period (1 day) eligible subjects will be admitted to the clinic. After completion of routine safety assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS), blood samples will be collected for the exploratory biomarker analyses, including potentially related to dementia, COPD, and OSA-related biomarkers and then subjects will enter the Randomization Phase.

Randomization Phase

In the Randomization Phase subjects will be randomized in treatment sequences A or B (OSA Cohort), or treatment sequences C or D (COPD Cohort) 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 (adults ≥45 and <65 years, vs elderly ≥65 to 90 years). A sufficient number of subjects will be randomized to ensure that, for each Cohort, 20 evaluable adult subjects and 10 evaluable elderly subjects complete the study. Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio and enter Treatment Period 1.

Treatment Periods 1 and 2

Subjects will remain overnight in the sleep laboratory. On Day 1, 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. If SpO2 is <80% for ≥20% of TST during the first night of treatment, the subject must be early terminated. Continuing subjects will be provided with study medication to be administered for 6 consecutive nights at home and will be instructed to take the medication immediately (within 5 minutes) before bedtime and then subjects may leave the clinic after the investigator determines that it is safe for them to do so.

On Day 5 (with a window of ±2 days to accommodate a weekend), the site will telephone the subject to assess adverse events (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.

Subjects will return to the clinic after 6 consecutive nights of administering study drug at home, subjects will return to the clinic and receive 8th dose of study drug at the sleep laboratory within 5 min before the lights off and will remain overnight in the sleep laboratory. A predose (trough) PK

blood sample will be taken within 1 hour before dosing. The following morning, blood samples will be collected for PK and exploratory biomarker assessments. Routine safety assessments will also conducted. 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, including re-review of inclusion and exclusion criteria, and oxygen desaturation. However, spirometry will only be performed during the Screening Period (revised per Amendment 01). Upon completion of Treatment Period 2, the subject will be discharged from the clinic and enter the Follow-up Period.

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

Follow-up Period

During the Follow-up Period (approximately 28 days), subjects will not receive any 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.

If subjects discontinue prematurely, they will undergo an Early Termination (ET) Visit and will then be followed for 28 days, after which an EOS visit should be scheduled.

Number of Subjects

OSA Cohort: A sufficient number of subjects will be randomized in order to ensure that a total of 30 evaluable subjects complete the study (20 evaluable adult subjects [≥45 and <65 years] and 10 evaluable elderly subjects [≥65 to 90 years]). Discontinued subjects may be replaced to ensure 20 adults and 10 elderly subjects complete both Treatment Periods. However, subjects who discontinue for a serious adverse drug reaction (SADR) cannot be replaced.

COPD Cohort: A sufficient number of subjects will be randomized in order to ensure that a total of 30 evaluable subjects complete the study (20 evaluable adult subjects (≥45 and <65 years) and 10 evaluable elderly subjects [≥65 to 90 years]). Discontinued subjects may be replaced to ensure 20 adults and 10 elderly subjects complete both Treatment Periods. However, subjects who discontinue for a SADR cannot be replaced.

Inclusion Criteria

Inclusion Criteria (OSA and COPD Cohorts)

1. Male or female, age ≥45 and ≤90 at the time of informed consent
2. Voluntary agreement and ability to provide written informed consent
3. Body mass index (BMI) <40 kg/m^2
4. Reports habitually sleeping for at least 5.5 hours per night
5. Reports habitual bedtime between 21:00 and midnight
6. Agrees to stay in bed for 7 hours per night for the duration of the study
7. At Screening Visit 2: Has completed the sleep diary for at least 5 consecutive nights
8. At Screening Visit 2: Confirmation of MHB between 21:00 and midnight (sleep diary)

Additional Inclusion Criteria (OSA Cohort)

9. Moderate to severe OSA diagnosed according to the criteria of the International Classification of Sleep Disorders (ICSD), confirmed by PSG (home sleep testing by portable monitor is acceptable) within the previous 5 years or a repeated PSG during screening
10. On screening PSG: moderate OSA (defined as 15≤ AHI <30) or severe OSA (defined as AHI ≥30 per hour)

11. SpO2 ≥94% assessed as part of vital signs at Screening Visit 1

Additional Inclusion Criteria (COPD Cohort)

12. Screening spirometry performed as per the GOLD recommendations
13. On screening spirometry, based on post-bronchodilator Forced Expiratory Volume in 1 second (FEV1):
    - FEV1/Forced Vital Capacity (FVC) <0.70 and one of the following:
      - 50%≤ FEV1 <80% predicted (GOLD 2 Classification for moderate COPD) or
      - 30%≤ FEV1 <50% predicted (GOLD 3 Classification for severe COPD)
11. Moderate to severe COPD according to medical history and screening spirometry as per the GOLD criteria (GOLD 2019)
12. On screening PSG
    - AHI<15
    - SpO2 during wakefulness >90% (both supine and sitting)
    - SpO2 during sleep ≥80% for at least 75% of the recording period with no more than 5 continuous minutes <80% and with no SpO2 readings <70%

Exclusion Criteria (OSA and COPD Cohorts)

1. Females of childbearing potential

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

2. A current diagnosis of restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorder, or narcolepsy
3. 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
4. A history of symptoms of REM Behavior Disorder, sleep-related violent behavior, sleep-driving, or sleep-eating, or symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study
5. 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
6. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening
7. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS)
8. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS) within 10 years of Screening
9. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
10. Hypersensitivity to the study drug or any of the excipients
11. Used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before the screening PSG

12. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
13. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
14. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years
15. History of drug or alcohol dependency or abuse within approximately the last 2 years
16. Use of illegal recreational drugs (includes marijuana, regardless of whether prescribed for medicinal use)
17. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer preceding informed consent
18. Previously participated in other clinical trial of lemborexant
19. Exposure within the last 14 days to an individual with confirmed or probable corona virus disease 2019 (COVID-19) or symptoms within the last 14 days that are on the most recent Centers for Disease Control and Prevention (CDC) list of COVID symptoms or any other reason to consider the subject at potential risk for an acute COVID-19 infection (revised per Amendment 01)

Additional Exclusion Criteria (OSA Cohort)

20. SpO2 <80% for ≥5% of TST during the screening PSG
21. Use of a continuous positive airway pressure (CPAP) device or dental appliance within 2 weeks of the screening PSG, and does not agree to abstain from the use of a CPAP device or dental appliance from the Screening Visit through the last study visit
22. Current evidence of a clinically significant, active respiratory disorder other than OSA. This includes bronchiectasis, emphysema, asthma, COPD, 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.
23. Current evidence of other clinically significant disease (eg, 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.

Additional Exclusion Criteria (COPD Cohort)

24. Use of continuous (>16 h/day) oxygen therapy
25. Use of oxygen therapy during PSG
26. Determination that, in the opinion of the investigator, removal of oxygen therapy could affect the subject's safety or interfere with the study assessments
27. Recent changes to COPD medications or recent acute exacerbation of COPD (ie, needing hospitalization or treatment with oral corticosteroids and/or antibiotics) within 3 months of enrollment (revised per Amendment 01)
28. On screening spirometry:
    - FEV1/FVC ≥0.70
    - FEV1 ≥80% predicted (GOLD 1 Classification for mild COPD)

- FEV1 <30% predicted (GOLD 4 Classification for very severe COPD)

29. On screening PSG:
    - Moderate to severe OSA (AHI ≥15)
    - SpO2 <90% during wakefulness (supine and sitting)
    - SpO2 during sleep <80% for 25% or more of the recording with >5 consecutive minutes <80% and any SpO2 reading <70%
30. ECG evidence of right ventricular hypertrophy or right heart failure
31. Screening hematocrit >55%
32. Use of a CPAP device or dental appliance within 2 weeks of the screening PSG, and does not agree to abstain from the use of a CPAP device or dental appliance from the Screening Visit through the last study visit
33. Current evidence of a clinically significant, active respiratory disorder other than COPD and mild OSA. This includes 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.
34. Current evidence of other clinically significant disease other than COPD and mild OSA (eg, 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.

Study Treatment(s)

The following treatments will be administered to subjects in this study:

- lemborexant 10-mg film-coated tablets, taken immediately (within 5 minutes) before "lights off"
- lemborexant-matched placebo tablets, taken immediately (within 5 minutes) before "lights off"

Duration of Treatment

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

Concomitant Drug/Therapy

Subjects with OSA 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 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 and moderate cytochrome P450 (CYP)3A inhibitors and strong and moderate CYP3A inducers. 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 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 and moderate CYP3A inhibitors and strong and moderate CYP3A inducers will not be permitted at any time for any duration during the study.

Assessments

Screening Assessments

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.
Spirometry will be performed for subjects evaluated for the COPD Cohort as per GOLD recommendations. Spirometry assesses the integrated mechanical function of the lung, chest wall, and respiratory muscles by measuring the total volume of air exhaled from a full lung to maximal expiration. Spirometry is the most reproducible and reliable measurement of airflow limitation, and is required to establish the diagnosis of COPD based on the measurement of FEV1 and FVC. Spirometry is also used to classify COPD severity (GOLD 2019).

Efficacy Assessments

Not applicable

Pharmacokinetic Assessments

A single blood sample for plasma concentrations of lemborexant 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.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

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
- Desaturation: Decrease in the mean SpO2 of ≥3% (over the last 120 seconds) that lasts for at least 10 seconds (revised per Amendment 01)

- ODI: (oxygen desaturations ≥3%×60)/TST (ie, the average number of oxygen desaturations ≥3% per hour of sleep), as defined by the American Academy of Sleep Medicine (revised per Amendment 01)

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 2 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.

Biomarker Assessments

Blood Biomarkers

Blood samples will be collected as indicated in the Schedule of Assessment for the exploratory analyses of biomarkers potentially related to dementia, COPD, and OSA.

Pharmacogenomic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations.

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.

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 method.

Statistical Methods

Study Endpoints

Primary Endpoint (OSA Cohort)

- AHI on Day 8 of treatment

Secondary Endpoint (OSA Cohort)

- AHI on Day 1 of treatment
- Mean SpO2 during TST on Day 1 and Day 8 of treatment
- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
- Mean ODI on Days 1 and 8 of treatment (revised per Amendment 01)
- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment (revised per Amendment 01)

Primary Endpoint (COPD Cohort)

- Mean SpO2 during TST on Day 8 of treatment

Secondary Endpoint (COPD Cohort)

- Mean SpO2 during TST on Day 1 of treatment
- AHI on Day 1 and Day 8 of treatment
- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
- Mean ODI on Days 1 and 8 of treatment (revised per Amendment 01)
- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment (revised per Amendment 01)

Exploratory Endpoints (OSA and COPD Cohorts)

- Mean SpO2 during REM sleep, NREM and wake on Day 1 (and Day 8 for OSA Cohort) of treatment
- AHI during REM and NREM sleep on Day 1 and Day 8 of treatment
- AHI separately for adult and elderly subjects at all days assessed
- Mean SpO2 during TST separately for adult and elderly subjects at all days assessed
- Lemborexant and its metabolites plasma concentrations at all days assessed
- Change from baseline for biomarkers will be evaluated

Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of test drug and had at least 1 quantifiable plasma concentration after dosing with lemborexant.

The Pharmacodynamic (PD) Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PD data to derive at least 1 primary PD parameter.

Efficacy Analyses

Not applicable

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lemborexant and its metabolites plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant plasma concentrations.

Pharmacodynamic Analyses

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

Analysis for the Primary Endpoint

OSA Cohort: Mean AHI will be analyzed on the PD analysis set using repeated measures analysis of variance (ANOVA), for Day 8 of each treatment period. The model will include fixed effects for age group, sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: Least square (LS) means, difference in LS mean of lemborexant 10 mg compared to placebo, a 2-sided 90% CI (equivalent to a 1-sided upper 95% CI) for the true mean difference (lemborexant − placebo) in AHI. If the upper bound of the 1-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 moderate to severe OSA compared with placebo. Further details will be provided in the statistical analysis plan (revised per Amendment 01).

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

COPD Cohort: Mean SpO2 will be analyzed on the PD analysis set using repeated measures ANOVA, of values on Day 1 of each treatment for subjects in the PD analysis set. The model will include fixed effects for age group, 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 2-sided 90% CI (equivalent to a 1-sided lower 95% CI) for the true mean difference (lemborexant − placebo) in SpO2. If the lower bound of the 1-sided 95% CI of the treatment difference of SpO2 is greater than -2 (for active – placebo), this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO2 compared to placebo. Further details will be provided in the statistical analysis plan (revised per Amendment 01).

Analysis for the Secondary Endpoints

The secondary endpoints will be analyzed using the same model as the primary endpoint.

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.

Pharmacogenomic Analyses

Not applicable

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.

Interim Analyses

No interim analysis is planned.

Sample Size Rationale

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 el., 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 less than 5.

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

COPD Cohort:
A 2% decrease in mean SpO2 during TST is considered a clinically meaningful change. For the primary hypothesis (mean SpO2 during TST on Day 8), assuming a true within subject variance of 1.07% for mean SpO2, a total of 30 subjects completing the crossover study, and significance level alpha 0.05, there is 0.95 probability that the lower bound of the 90% confidence interval (CI) for the true mean difference in mean SpO2 (LEM- placebo) on Day 8 would be greater than 2 percent points, if the true difference is 1 percent point. The true difference could be as low as 1.23% and the study still would have had 80% power to support the hypothesis.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
AHI	apnea hypopnea index
BMI	body mass index
BP	blood pressure
CA	Competent Authority
CDC	Centers for Disease Control and Prevention
CPAP	continuous positive airway pressure
COPD	Chronic obstructive pulmonary disease
COVID-19	Corona Virus Disease 2019
CRAs	clinical research associates
CRF	case report form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	curriculum vitae
CYP	cytochrome P450
EMG	electromyography
EOG	electrooculography
EOS	end of study
ET	early termination
FEV1	Forced Expiratory Volume in 1 Second
FVC	forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
ICF	informed consent form
ICH	International Council for Harmonisation
ICSD	International Classification of Sleep Disorders
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LEM	lemborexant
LNH	low/normal/high

Abbreviation	Term
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MHB	mean habitual bedtime
NREM	non- rapid eye movement
ODI	oxygen desaturation index
OSA	obstructive sleep apnea
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic
PLMAI	Periodic Limb Movement with Arousal Index
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	postmarketing requirement
PSG	polysomnography
PT	preferred term
REM	rapid eye movement
SADR	serious adverse drug reaction
SAE	serious adverse event
SaO2	arterial oxygen saturation
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SpO2	peripheral capillary oxygen saturation
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TST	total sleep time
WHO DD	World Health Organization Drug Dictionary

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 (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 associates [CRAs], 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 IRBs 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 or designee should notify the IRB and Competent Authority (CA) 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 CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF 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. 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 or designee 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 and Contract Research Organization (CRO) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

Lemborexant (LEM) (1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide), also known as E2006, is an orally-administered, novel competitive dual orexin receptor antagonist (DORA) that has been developed for the treatment of insomnia 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 apnea hypopnea index (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.

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).

It has long been known that sleep is disturbed in patients with chronic obstructive pulmonary disease (COPD). Insomnia is a comorbid condition in about 17% of patients with COPD. There are general concerns about administering sedative-hypnotics to patients with compromised respiratory function, since traditional sedative-hypnotics that bind to the benzodiazepine receptor at the gamma amino butyric acid (GABA)-A complex (eg, tri-azolam, flurazepam) have the potential to cause depression of central respiratory drive and decreased muscle tone in the upper airways. Research suggests that there may be differences among benzodiazepine receptor agonists with regard to respiratory safety. Consequently, the respiratory safety of any new sleep-promoting agent should be carefully evaluated (Sun, et al., 2015).

Orexin receptor antagonism represents a new approach to the treatment of insomnia. Orexin receptor antagonists may promote sleep by selectively blocking the brain's orexin-mediated wake system thereby enabling the transition to sleep. Orexin neurons originate in the lateral hypothalamus and project throughout the brain, including to respiratory centers in the brain stem. This suggests that orexin may have a role in regulating respiration (Sun, et al., 2015).

7.1 Compound Overview

Lemborexant (LEM) is a novel competitive dual orexin receptor antagonist that is approved for the treatment of insomnia by the Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) and under development for irregular sleep-wake rhythm disorder. The clinical development program established the safety, tolerability, and efficacy (both short- and long-term) of LEM versus placebo in adult and elderly subjects, including demonstration of respiratory safety in healthy volunteers and subjects with mild OSA (E2006-A001-102; Study 102).

7.2 Clinical Experience

Study 102 was a randomized, double-blind, placebo-controlled, crossover study to evaluate the respiratory safety of LEM in adult and elderly (≥65 to 90 years) healthy subjects and adult and elderly subjects with mild OSA. In healthy adult and elderly subjects and subjects with mild OSA, compared with placebo, LEM did not decrease peripheral oxygen saturation (SpO2) during total sleep time (TST) after a single dose of treatment, increase the proportion of subjects with at least 1 incident of desaturation (defined as SpO2 <90% for at least 30 seconds during TST compared to placebo, increase the percentage of TST during which SpO2 was <90%; or increased the AHI after a single dose of treatment. Study 102 concluded LEM was well tolerated in healthy adult and elderly subjects, as well as subjects with mild OSA. The approved prescribing information for LEM (Dayvigo®) states that: "*In a study of patients with mild OSA (AHI <15 events per hour of sleep), DAYVIGO did not increase the frequency of apneic events or cause oxygen desaturation.*"

7.3 Study Rationale

Per the DAYVIGO approval letter (20 Dec 2019) Eisai was tasked with specific Postmarketing Requirements (PMR), including a request to conduct a randomized, double-blind, placebo-controlled study to evaluate the short-term respiratory safety of LEM in subjects with moderate to severe OSA and in subjects with moderate to severe COPD (PMR 3753-1). The following study is proposed to fulfill this PMR.

8 STUDY OBJECTIVES

8.1 Primary Objective(s)

OSA Cohort:

- Using PSG, determine whether lemborexant increases the AHI on Day 8 of treatment in adult and elderly subjects (adults ≥45 to <65 years; elderly ≥65 to 90 years) with moderate to severe obstructive sleep apnea (OSA) compared with placebo

COPD Cohort:

- Using pulse oximetry, determine whether lemborexant decreases mean SpO2 during TST on Day 8 of treatment in adult and elderly subjects (adults ≥45 to <65 years; elderly ≥65 to 90 years) with moderate to severe COPD compared with placebo

8.2 Secondary Objective(s)

OSA Cohort:

- Using PSG, determine whether lemborexant increases the AHI on Day 1 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant decreases the mean SpO2 during TST on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the SpO2 is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the mean oxygen desaturation index (ODI) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Using pulse oximetry, determine whether lemborexant increases the absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Evaluate safety and tolerability of lemborexant compared with placebo

COPD Cohort:

- Using pulse oximetry, determine whether lemborexant decreases mean SpO2 during TST on Day 1 of treatment compared with placebo
- Using PSG, determine whether lemborexant increases the AHI on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the percentage of TST during which the SpO2 is <90%, <85%, and <80% on Days 1 and 8 of treatment compared with placebo
- Using pulse oximetry, determine whether lemborexant increases the mean ODI on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Using pulse oximetry, determine whether lemborexant increases the absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment compared with placebo (revised per Amendment 01)
- Evaluate safety and tolerability of lemborexant compared with placebo

8.3 Exploratory Objective(s)

OSA and COPD Cohorts:

Explore the effects of lemborexant compared with placebo on the following for Days 1 and 8 of treatment:

- The mean SpO2 during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
- AHI during REM and NREM sleep
- Determine whether lemborexant increases the AHI, and decreases the mean SpO2 during TST separately for adult and elderly subjects
- Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10)
- Explore the effect of lemborexant on blood biomarkers potentially related to dementia, OSA, and/or COPD

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

In both the OSA and COPD Cohorts, this will be a randomized, double-blind, placebo-controlled, 2-period crossover study. 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. In the Randomization Phase subjects will be randomized in treatment sequences A or B (OSA Cohort), or treatment sequences C or D (COPD Cohort) consisting of 2 Treatment Periods, each of 8 days duration, separated by a washout interval of at least 14 days, and a Follow-up Period of approximately 28 days. Twenty-eight days after the final study dose, there will be an end of study (EOS) Visit.

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

Approximately 75 subjects each will be screened for OSA and COPD cohorts in order to ensure that a total of 30 evaluable subjects complete the study in each cohort (20 evaluable adult subjects [≥45 and <65 years] and 10 evaluable elderly subjects [≥65 to 90 years]). Discontinued subjects may be replaced to ensure 20 adults and 10 elderly subjects complete both Treatment Periods. However, subjects who discontinue for a serious adverse drug reaction (SADR) cannot be replaced.

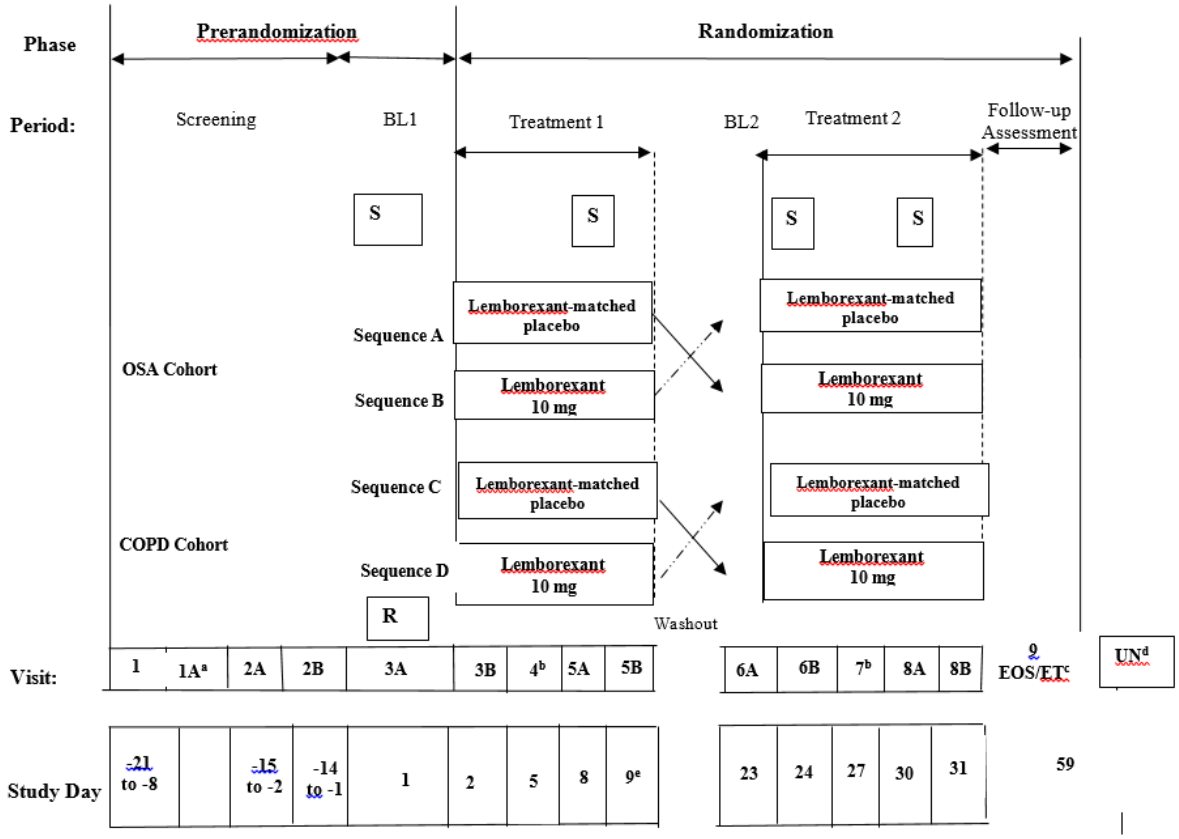

Figure 1 Study Design for OSA and COPD Cohorts (revised per Amendment 01)

BL1 = Period 1 Baseline, BL2 = Period 2 Baseline, COPD = chronic obstructive pulmonary disease, EOS = End of Study, ET = Early Termination, OSA = Obstructive sleep apnea, S = Sleep laboratory, R = Randomization, UN = Un-Scheduled visit.

a: Visit 1A only applies to subjects being evaluated for the COPD Cohort, in whom spirometry is required. Spirometry may be performed at the study site, or offsite, so long as a final report is available for review at the study site by Visit 2

b: Telephone visit

c: Assessments as shown will be conducted at the EOS visit and for subjects who discontinue the study early after Visit 3. 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 ET Visit and will then be followed for 28 days, after which, an EOS visit should be scheduled.

d: The assessments at an Unscheduled Visit will be conducted at the Investigator's discretion.

e: Visit must be followed by a washout interval of at least 14 days in duration. This may be extended by up to 2 days if necessary to accommodate a weekend, in which case, subsequent visits will be up to 2 days later than target.

9.1.1 Prerandomization/Pretreatment Phase

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

9.1.1.1 Screening Period

The Screening Period will begin no more than 21 days before the subject is randomized and during which 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. Subjects eligible for the COPD Cohort will then undergo screening spirometry between Visit 1 and Visit 2 (designated Visit 1A), which may be performed at the study site, or offsite, so long as a final report is available for review at the study site by Visit 2. Spirometry will be performed based on Global Initiative for Obstructive Lung Disease (GOLD) recommendations (Appendix 2).

After at least 6 days of the initial Screening visit, (to allow subjects the opportunity to complete the sleep diary for at least 5 nights), subjects will return to the clinic for the second Screening Visit to undergo PSG. For subjects being evaluated for the COPD Cohort, results of screening spirometry will also be reviewed.

Subjects who continue to meet the eligibility criteria will remain overnight in the sleep laboratory. The mean 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 severity (only mild for the OSA Cohort, and moderate to severe for the COPD Cohort), 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 Baseline Period.

9.1.1.2 Baseline Period

At the Baseline Period (1 day) eligible subjects will be admitted to the clinic. After completion of routine safety assessments, including the Columbia-Suicide Severity Rating Scale (C-SSRS), blood samples will be collected for the exploratory analyses related to potential dementia, COPD, and OSA-related biomarkers. Subject will then enter the Randomization Phase.

9.1.2 Randomization/Treatment Phase

In the Randomization Phase, subjects will be randomized into treatment sequence A or B (OSA Cohort), or treatment sequence C or D (COPD Cohort) 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 (adults ≥45 and <65 years, vs elderly ≥65 to 90 years). A sufficient number of subjects will be randomized to ensure that, for each Cohort, 20 evaluable adult subjects and 10 evaluable

elderly subjects complete the study. Within each age stratum, subjects will be randomized to 1 of the 2 treatment sequences in a 1:1 ratio and enter Treatment Period 1.

Subjects will remain overnight in the sleep laboratory. 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 (Table 4).

Subjects will be provided with study medication to be administered for 6 consecutive nights at home, and will be instructed to take the medication immediately (within 5 minutes) before bedtime. Subjects will also be instructed on study restrictions related to prohibited medications/drugs, caffeine and alcohol, and the prohibitions regarding the use of continuous positive airway pressure (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 study physician in case of any new complaints or exacerbation of current symptoms.

On Day 5 (with a window of ±2 days to accommodate a weekend), 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 and receive 8th dose of study drug at the sleep laboratory within 5 min before the lights off 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 and urine drug test), in addition to which, a blood sample for pre-dose (trough) PK will be taken within 1 hour before dosing. The following morning, blood samples will be collected for PK, and exploratory biomarker assessments. Routine safety assessments will also conducted, as indicated in the Schedule of Procedures/Assessments (Table 4). 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. After the washout interval, subjects will return to the clinic for Treatment Period 2, which will follow the same schedule and procedures as did in Treatment Period 1, including re-review of inclusion and exclusion criteria, and oxygen desaturation. However, spirometry will only be performed during the Screening Period (revised per Amendment 01).

At specified visits throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments, including 12-lead ECG, physical examination, vital signs, weight, hematology, blood clinical chemistry analysis, urinalysis,

reporting of AEs, and assessment of suicidality. At each clinic visit, subjects will also undergo a urine drug screen.

9.1.2.1 Follow-Up Period

During the Follow-up Period (approximately 28 days), subjects will not receive any 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.

If subjects discontinue prematurely, they will undergo an Early Termination (ET) Visit and will then be followed for 28 days, after which, an EOS visit should be scheduled.

9.2 Discussion of Study Design, Including Choice of Control Groups

Dose Selection

The approved dose of LEM 10 mg was chosen based on the safety and efficacy studies from the clinical development program.

Justification of the Endpoints

The primary analysis in the OSA Cohort compares the mean AHI (assessed by PSG) on the final night of LEM dosing with the AHI on the final night of placebo dosing. The AHI is the index by which OSA is diagnosed, is used to categorize the severity of disease, and is the standard primary endpoint in clinical studies of the safety of drugs in patients with OSA; for example, this was used for LEM Study 102, suvorexant (Sun, et al., 2016), ramelteon (Kryger, et al., 2007), and eszopiclone (Rosenberg, et al., 2007). Like the study of suvorexant, Study 113 will use the mean AHI at the end of each treatment period as the primary endpoint, as LEM will have reached steady state.

The primary analysis in the COPD Cohort compares mean SpO2 over total sleep time (TST) on the final night of LEM dosing with mean SpO2 during TST on the final night of placebo dosing. Specifically, a 2% decrease in mean SpO2 during TST is considered a clinically meaningful change. SpO2 measures hypoxia, which can serve as a proxy for hypoventilation during sleep (Piper and Yee, 2014). In the ramelteon study of subjects with moderate to severe COPD (Kryger, et al., 2009), the mean SpO2 during TST at baseline was 92.6%, thus a 2% or greater decrease from 92% could result in hypoxia (SpO2 <90%). Of note, this was also used as the primary endpoint in the suvorexant study (Sun, et al., 2015).

Justification of the sample size for the OSA cohort

In the suvorexant study, 26 subjects with mild to moderate OSA were studied; in Study 102, 30 subjects with mild OSA were evaluated. This was acceptable to FDA and PMDA. Thus, the proposed sample size for Study 113 OSA is 30 (Sun, et al., 2016).

Inclusion and Exclusion Criteria for the OSA and COPD Cohorts

The eligibility criteria in Study 113 are largely standard for safety studies in subjects, with particular criteria that are standard for studies of sleep agents (exclusion of significant periodic limb movement disorder or parasomnias; certain restrictions on habitual bedtime). Insomnia disorder is not specifically excluded unless subjects habitually sleep less than 5.5 hours. The screening PSG will be key for inclusion, since subjects tend to sleep less well in a sleep laboratory than at home. This is important since the AHI tends to be higher during REM sleep, which is more frequent during the second half of the night, the time when elderly poor sleepers tend to be awake.

Of note, CPAP and oral devices will be prohibited throughout the study. The study requires uncorrected values for AHI. The phenomenon of "CPAP washout" has been reported, in which, following cessation of CPAP use, AHI increases gradually over days or weeks (Vroegop, et al., 2015). Although the existence of this phenomenon is not universally accepted, there is no doubt that daytime sleepiness increases when CPAP is stopped, and those patients with OSA will accommodate to the increased levels of sleepiness, but that takes time, and the duration varies among patients. To avoid dosing with LEM (which may cause somnolence during the day in some subjects) against an unstable baseline of daytime sleepiness, Study 113 requires that CPAP not be used from 2 weeks before the screening PSG until the end of the second treatment period. This should not interfere with the medical care of OSA patients, or be a significant impediment to recruitment; many patients do not tolerate CPAP, such that non-compliance rates are high, as stated above. Further, the exclusion criterion specifies that there must not be a requirement that subjects use CPAP during the study, thereby excluding any for whom CPAP is a medical necessity. Whether subjects had been prescribed CPAP or other treatments for OSA in the past will be noted at Screening.

Inclusion and Exclusion criteria for the COPD Cohort

The COPD cohort will include subjects with moderate to severe COPD and an AHI <15 based on PSG. A diagnosis of mild OSA is permissible, as OSA is a common co-morbidity in patients with COPD, and high-level evidence for the benefit of mild OSA treatment is sparse (Gay, et al., 2006). Subjects will also be required to have a SpO2 during wakefulness greater than 90% (both supine and sitting), and a SpO2 during sleep ≥80% for at least 75% of the recording period with no more than five continuous minutes less than 80% and with no SpO2 readings less than 70%. These criteria are similar to the ramelteon study in subjects with moderate to severe COPD (Kryger, et al., 2009). Subjects who use continuous oxygen therapy (>16 hours per day) or who, in the opinion of the investigator, the removal of oxygen therapy could affect the subject's safety or interfere with the study assessments, are also excluded, which also aligns with prior respiratory safety studies in COPD.

9.3 Selection of Study Population

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

Subjects must meet all of the following criteria to be included in this study (OSA and COPD cohorts):

1. Male or female, age ≥45 and ≤90 at the time of informed consent
2. Voluntary agreement and ability to provide written informed consent
3. Body mass index (BMI) <40 kg/m^2
4. Reports habitually sleeping for at least 5.5 hours per night
5. Reports habitual bedtime between 21:00 and midnight
6. Agrees to stay in bed for 7 hours per night for the duration of the study
7. At Screening Visit 2: Has completed the sleep diary for at least 5 consecutive nights
8. At Screening Visit 2: Confirmation of MHB between 21:00 and midnight (sleep diary)

Additional Inclusion Criteria (OSA Cohort)

9. Moderate to severe OSA diagnosed according to the criteria of the ICSD, confirmed by PSG (home sleep testing by portable monitor is acceptable) within the previous 5 years or a repeated PSG during screening
10. On screening PSG: moderate OSA (defined as 15≤AHI<30) or severe OSA (defined as AHI ≥30 per hour)
11. SpO2 ≥94% assessed as part of vital signs at Screening Visit 1

Additional Inclusion Criteria (COPD Cohort)

12. Screening spirometry performed as per the GOLD recommendations
13. On screening spirometry, based on post-bronchodilator Forced Expiratory Volume in 1 second (FEV1):
    - FEV1/Forced Vital Capacity (FVC) < 0.70 and one of the following:
      - 50%≤ FEV1 <80% predicted (GOLD 2 Classification for moderate COPD) or
      - 30%≤ FEV1 <50% predicted (GOLD 3 Classification for severe COPD)
14. Moderate to severe COPD according to medical history and screening spirometry as per the GOLD criteria (GOLD 2019)
15. On screening PSG
    - AHI<15
    - SpO2 during wakefulness >90% (both supine and sitting)
    - SpO2 during sleep ≥80% for at least 75% of the recording period with no more than five continuous minutes <80% and with no SpO2 readings <70%

9.3.2 Exclusion Criteria

1. Females of childbearing potential

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie,

bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

2. A current diagnosis of restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorder, or narcolepsy
3. 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
4. A history of symptoms of REM Behavior Disorder, sleep-related violent behavior, sleep-driving, or sleep-eating, or symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study
5. 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
6. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening
7. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS)
8. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS) within 10 years of Screening
9. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
10. Hypersensitivity to the study drug or any of the excipients
11. Used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before the screening PSG
12. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
13. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
14. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years
15. History of drug or alcohol dependency or abuse within approximately the last 2 years
16. Use of illegal recreational drugs (includes marijuana, regardless of whether prescribed for medicinal use)
17. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer preceding informed consent
18. Previously participated in other clinical trial of lemborexant
19. Exposure within the last 14 days to an individual with confirmed or probable corona virus disease 2019 (COVID-19) or symptoms within the last 14 days that are on the most

recent Centers for Disease Control and Prevention (CDC) list of COVID symptoms or any other reason to consider the subject at potential risk for an acute COVID-19 infection (revised per Amendment 01)

Additional Exclusion Criteria (OSA Cohort)

20. SpO2 <80% for ≥5% of TST during the screening PSG
21. Use of a CPAP device or dental appliance within 2 weeks of the screening PSG, and does not agree to abstain from the use of a CPAP device or dental appliance from the Screening Visit through the last study visit
22. Current evidence of a clinically significant, active respiratory disorder other than OSA. This includes bronchiectasis, emphysema, asthma, COPD 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.
23. Current evidence of other clinically significant disease (eg, 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.

Additional Exclusion Criteria (COPD Cohort)

24. Use of continuous (>16 h/day) oxygen therapy
25. Use of oxygen therapy during PSG
26. Determination that, in the opinion of the investigator, removal of oxygen therapy could affect the subject's safety or interfere with the study assessments
27. Recent changes to COPD medications or recent acute exacerbation of COPD (ie, needing hospitalization or treatment with oral corticosteroids and/or antibiotics) within 3 months of enrollment (revised per Amendment 01)
28. On screening spirometry:
    - FEV1/FVC ≥0.70
    - FEV1 ≥80% predicted (GOLD 1 Classification for mild COPD)
    - FEV1 <30% predicted (GOLD 4 Classification for very severe COPD)
29. On screening PSG:
    - Moderate to severe OSA (AHI ≥15)
    - SpO2 <90% during wakefulness (supine and sitting)
    - SpO2 during sleep <80% for 25% or more of the recording with >5 consecutive minutes <80% and any SpO2 reading <70%
30. ECG evidence of right ventricular hypertrophy or right heart failure

31. Screening hematocrit >55%
32. Use of a CPAP device or dental appliance within 2 weeks of the screening PSG, and does not agree to abstain from the use of a CPAP device or dental appliance from the Screening Visit through the last study visit
33. Current evidence of a clinically significant, active respiratory disorder other than COPD and mild OSA. This includes 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.
34. Current evidence of other clinically significant disease other than COPD and mild OSA (eg, 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.

9.4 Treatments

9.4.1 Treatments Administered

The following treatments will be administered to subjects in this study:

- lemborexant 10-mg film-coated tablets, taken immediately (within 5 minutes) before "lights off"
- lemborexant-matched placebo tablets, taken immediately (within 5 minutes) before "lights off"

Table 1 Treatments Administered (OSA Cohort)

Treatment Sequence	Treatment Periods in the OSA Cohort	
	1 (8 nights)	2 (8 nights)
A	lemborexant-matched placebo	lemborexant 10 mg
B	lemborexant 10 mg	lemborexant-matched placebo

Table 2 Treatments Administered (COPD Cohort)

Treatment Sequence	Treatment Periods in the COPD Cohort	
	1 (8 nights)	2 (8 nights)
C	lemborexant-matched placebo	lemborexant 10 mg
D	lemborexant 10 mg	lemborexant-matched placebo

9.4.2 Identity of Investigational Product(s)

Lemborexant 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 sponsor will provide the study drug packaged as double-blinded supplies. Each subject's study drug will consist of lemborexant tablets supplied in bottles.

9.4.2.1 Chemical Name of E2006

- 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

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

Lemborexant will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to 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

The approved dose of LEM 10 mg was chosen based on the safety and efficacy studies from the clinical development program.

9.4.5 Selection and Timing of Dose for Each Subject

All randomized subjects will receive lemborexant 10 mg or placebo for 8 nights in each treatment period per the randomization scheme for OSA and COPD cohorts. The Treatment Periods will be separated by a washout interval of at least 14 days.

Subjects will receive the 1st dose of study treatment at the sleep laboratory within 5 min before the lights off and will remain overnight in the sleep laboratory. Subjects will be provided with the study medication to be administered for 6 consecutive nights at home, and will be instructed to take the medication immediately (within 5 minutes) before bedtime. After 6 consecutive nights of administering the study drug at home, subjects will return to the clinic and receive 8th dose of study drug at the sleep laboratory within 5 min before the lights off and remain overnight in the sleep laboratory.

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 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 by the sponsor. In addition, master code breaker reports or envelopes identifying the treatment group of each subject number will be provided to the site and to the sponsor in sealed envelopes. These code breaker reports or envelopes are not to be opened unless an emergency occurs and knowledge of the subject's randomization code may affect his/her medical treatment. 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 of opening the code breaker report or envelope and the reason for breaking the code. At the conclusion of the study, where possible, all unused drug supplies at the site, together with master code breaker reports or envelopes, are to be returned to the clinical supply vendor for final reconciliation and disposition.

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 case report form (CRF) or Non-Pharmacological Procedures CRF. The investigator will record on the AE CRF any AE for which the concomitant medication/therapy was administered.

Subjects with OSA 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 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 and moderate cytochrome P450 (CYP)3A inhibitors and strong and moderate CYP3A inducers. 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 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 and moderate CYP3A inhibitors and strong and moderate CYP3A inducers will not be permitted at any time for any duration during the study.

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 forgo 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. 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 for the institution where the study is to be conducted
- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB 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 FDA Form FDA 1572 or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number (if applicable) on the CV
- A signed and dated Clinical Trial 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 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 or designee, 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). 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 Screening Assessments

9.5.1.1.1 DEMOGRAPHY

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

9.5.1.1.2 MEDICAL HISTORY

Medical, surgical, psychiatric, and sleep history (including history of OSA, and its treatments, history of somnambulism, history of periodic limb movement disorder, restless leg syndrome, circadian rhythm disorder, and narcolepsy) and current medical conditions will be recorded at the Screening Visit. All medical and surgical history must be noted in the Medical History and Current Medical Conditions CRFs.

9.5.1.1.3 SLEEP DIARY

A paper sleep diary will be completed by the subjects within 1 hour of wake time on at least 5 consecutive mornings during screening, before Screening Visit 2. Sleep diaries will be reviewed to determine eligibility before or during check-in at Screening Visit 2.

9.5.1.1.4 SPIROMETRY

Spirometry will be performed for subjects evaluated for the COPD Cohort as per GOLD recommendations. Spirometry assesses the integrated mechanical function of the lung, chest wall, and respiratory muscles by measuring the total volume of air exhaled from a full lung to maximal expiration. Spirometry is the most reproducible and reliable measurement of airflow limitation, and is required to establish the diagnosis of COPD based on the measurement of FEV1 and FVC. Spirometry is also used to classify COPD severity (GOLD 2019).

9.5.1.2 Efficacy Assessments

Not applicable

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Collection and handling of PK, PD, and biomarker samples will be detailed in the central laboratory manual to be provided to clinical sites.

Pharmacogenomic assessments are not applicable for this study.

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

A single blood sample (4 mL) for determination of plasma concentrations of lemborexant and its metabolites M4, M9 and M10 will be taken at predefined visits (see Table 4). The time and date of the 2 most recent doses administered before each sample will be documented. Plasma concentrations of lemborexant and its metabolite will be quantified in active subjects only by liquid chromatography- tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Phamacodynamic 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
- Desaturation: Decrease in the mean SpO2 of ≥3% (over the last 120 seconds) that lasts for at least 10 seconds (revised per Amendment 01)
- ODI: (oxygen desaturations ≥3%×60)/TST (ie, the average number of oxygen desaturations ≥3% per hour of sleep), as defined by the American Academy of Sleep Medicine (revised per Amendment 01)

Transmissive pulse oximetry is a noninvasive method for monitoring 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 2 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.

Blood Biomarkers

Blood samples will be collected as indicated in the Schedule of Assessment (Table 4) for the exploratory analyses of biomarkers potentially related to dementia, COPD, and OSA.

Pharmacogenomic Assessments

Not applicable

9.5.1.4 Safety Assessments

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

9.5.1.4.1 ADVERSE EVENTS

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 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. Subject 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 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 9.5.1.4.7 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 serious adverse events (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 9.5.1.4.2 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.

9.5.1.4.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A 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

9.5.1.4.3 LABORATORY MEASUREMENTS

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

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Calcium, chloride, potassium, sodium
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	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by central laboratory. 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 will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Central laboratories 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 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF (see Section 9.5.4.3.2).

9.5.1.4.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 4) by a validated method. Blood pressure and pulse will be measured after the subject has been 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 before 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.

9.5.1.4.5 PHYSICAL EXAMINATIONS

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

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.

9.5.1.4.6 ELECTROCARDIOGRAMS

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

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.7 OTHER SAFETY ASSESSMENTS

Columbia-Suicide Severity Rating Scale

The C-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, at the Follow-up Visit, and as designated in the Schedule of Procedures/Assessments (Table 4).

9.5.1.5 Other Assessments

9.5.1.5.1 PREGNANCY TEST

A serum β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 consecutive months at Screening Visit 1. 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 4).

9.5.1.5.2 URINE DRUG AND COTININE TEST

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 4). This sample will be tested for common

drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, PCP, nicotine/cotinine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

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

Table 4 Schedule of Procedures/Assessments in Study E2006-A001-113

Phase	Prerandomization					Randomization										
Period	Screening				BL1	Treatment 1				BL2	Treatment 2				Follow-Up	
Visit	1	1A[a]	2A	2B	3A	3B	4[b]	5A	5B	6A	6B	7[b]	8A	8B	9 EOS/ET[c]	UN[d]
Study Day	−21 to −8		−15 to −2	−14 to −1	1	2	5	8	9[e]	23	24	27	30	31	59	
Demography	X															
Informed consent	X															
Inclusion/exclusion criteria	X		X		X					X						
Medical, surgical, psychiatric, and sleep History[f]	X															
Physical examination	X				X										X	X
Sleep diary[g]		----------→														
Urine drug test[h]	X		X		X			X		X			X			X
Height	X															
Weight	X														X	
Clinical laboratory tests[i]	X				X										X	X
PK blood sampling[j]						X		X	X		X		X	X		
Biomarker blood sampling[k]					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
Spirometry[n]		X														

Randomization					X											
Administer study drug in clinic[o]					X			X		X			X			
Dispense study drug					X					X						
Study drug taken at home						---------→					---------→					
PSG (with Pulse Oximetry)[p]			X		X[q]			X		X[r]			X			
C-SSRS	X				X										X	
Adverse events		----------→														
Prior and concomitant medications		----------→														
Admit to clinic			X		X			X		X			X			
Discharge from clinic				X		X			X		X			X		
Discharge from study															X	
Study drug return									X					X		

BL1 = Period 1 Baseline, BL2 = Period 2 Baseline, COPD = chronic obstructive pulmonary disease, 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: Visit 1A only applies to subjects being evaluated for the COPD Cohort, in whom spirometry is required. Spirometry may be performed at the study site, or offsite, so long as a final report is available for review at the study site by Visit 2.

b: Telephone visits.

c: Assessments as shown will be conducted at the EOS visit and for subjects who discontinue the study early after Visit 3. 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 ET Visit and will then be followed for 28 days, after which, an EOS visit should be scheduled.

d: The assessments at an Unscheduled Visit will be conducted at the Investigator's discretion.

e: Visit must be followed by a washout interval of at least 14 days in duration. This may be extended by up to 2 days if necessary to accommodate a weekend, in which case, subsequent visits will be up to 2 days later than target.

f: Sleep history will include: history of OSA, including treatments, history of somnambulism, history of 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 mean 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.

h: Urine drug screen 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 will be obtained at the following time points: within 1 hour predose in the clinic (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 will be recorded.

k: Blood samples (approximately 6 mL per timepoint) will be collected for determination of biomarkers

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, Visit 3A, and Visit 6A. (revised per Amendment 01)

n: Only for subjects being evaluated for the COPD cohort.

o: At Visit 3A, administered after all baseline assessments have been completed.

p: Screening PSG will include channels for assessment of symptoms of periodic limb movement disorder (PLMD).

q: PSG will occur after randomization and study drug administration during period BL1. (revised per Amendment 01)

r: PSG will occur after study drug administration during period BL2. (revised per Amendment 01)

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments is shown in Table 4.

9.5.2.3 Total Volume of Blood Sampling

Table 5 presents the number of blood samples and the total volume of blood that will be collected throughout the study for the OSA and COPD cohorts. 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 5 Summary of Blood Sample Volumes (OSA and COPD Cohorts)

	Sample Volume per Collection (mL)	Number of Collection Time Points	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening: 1 Baseline 1: 1 Follow-up: 1	12×3=36
PK blood sampling	4	Treatment Period 1: 3 Treatment Period 2: 3	4×6=24
Biomarker blood sampling	6	Baseline 1: 1 Baseline 2: 1 Treatment Period 1: 1 Treatment Period 2: 1	6×4=24
Total			84

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of respiratory safety and in particular, OSA and COPD.

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 SAEs, 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.

SAEs, regardless of causality assessment, must be collected 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 relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant 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 a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

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

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus 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 24 hours 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 24 hours 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 and Intentional Overdose, even if asymptomatic, are 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 Abnormal Hepatic Tests of Clinical Interest**

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as “nonserious.”

- Elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal

  AND

- Elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2X the upper limit of normal

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.5.4.3.3 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 4).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, 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.

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 9.5.1.4.1. 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 or Investigator and Site Information Form or Site Delegation Log 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

9.7.1.1.1 PRIMARY ENDPOINT (OSA COHORT)

- AHI on Day 8 of treatment

9.7.1.1.2 SECONDARY ENDPOINTS (OSA COHORT)

- AHI on Day 1 of treatment
- Mean SpO2 during TST on Day 1 and Day 8 of treatment
- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
- Mean ODI on Days 1 and 8 of treatment (revised per Amendment 01)

- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment (revised per Amendment 01)

9.7.1.1.3 PRIMARY ENDPOINT (COPD COHORT)

- Mean SpO2 during TST on Day 8 of treatment

9.7.1.1.4 SECONDARY ENDPOINTS (COPD COHORT)

- Mean SpO2 during TST on Day 1 of treatment
- AHI on Day 1 and Day 8 of treatment
- The percentage of TST during which the SpO2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
- Mean ODI on Days 1 and 8 of treatment (revised per Amendment 01)
- Absolute number of desaturations (≥3% reduction from Baseline SpO2) on Days 1 and 8 of treatment (revised per Amendment 01)

9.7.1.1.5 EXPLORATORY ENDPOINTS (OSA AND COPD COHORTS)

- Mean SpO2 during REM sleep, NREM and wake on Day 1 (and Day 8 for OSA Cohort) of treatment
- AHI during REM and NREM sleep on Day 1 and Day 8 of treatment
- AHI separately for adult and elderly subjects at all days assessed
- Mean SpO2 during TST separately for adult and elderly subjects at all days assessed

9.7.1.1.6 PHARMACOKINETIC ENDPOINT (OSA AND COPD COHORTS)

- Lemborexant plasma concentrations at all days assessed

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

- Change from baseline for biomarkers will be evaluated

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of test drug and had at least 1 quantifiable plasma concentration after dosing with lemborexant.

The Pharmacodynamic Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient PD data to derive at least 1 primary PD 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 OSA and COPD cohorts 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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by randomized treatment groups.

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 for all study drug groups combined using descriptive statistics. Continuous demographic and baseline variables include age, height, BMI, and weight variables; categorical variables include sex, age group (adults ≥45 to <65 years; elderly ≥ 65 to 90 years), 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) (March 2019 or later). 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 (PT). 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

OSA Cohort: Mean AHI will be analyzed on the PD analysis set using repeated measures ANOVA, for Day 8 of each treatment period. The model will include fixed effects for age group, sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: least square (LS) means, difference in LS mean of lemborexant 10 mg compared to placebo, a 2-sided 90% CI (equivalent to a 1-sided upper 95% CI) for the true mean difference (lemborexant − placebo) in AHI. If the upper bound of the 1-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 moderate to severe OSA compared with placebo. Further details will be provided in the statistical analysis plan (revised per Amendment 01).

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

COPD Cohort: Mean SpO2 will be analyzed on the PD analysis set using repeated measures ANOVA, of values on Day 1 of each treatment for subjects in the PD analysis set. 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 2-sided 90% CI (equivalent to a 1-sided lower 95% CI) for the true mean difference (lemborexant − placebo) in SpO2. If the lower bound of the 1-sided 95% CI of the treatment difference of SpO2 is greater than -2 (for active – placebo), this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO2 compared to placebo. Further details will be provided in the statistical analysis plan (revised per Amendment 01).

Analysis for the Secondary Endpoints

The secondary endpoints will be analyzed using the same model as the primary endpoint.

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 secondary endpoints.

Pharmacogenomic Analyses:

Not applicable

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, 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 treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and the C-SSRS. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

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 by treatment for OSA and COPD cohorts using descriptive statistics.

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 Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.1) lower level term (LLT) closest to the verbatim term. The linked MedDRA 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 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 (adults ≥45 and <65 years; elderly ≥65 to 90 years), sex (male, female), and race (white, black, other) if there are sufficient numbers in the category.

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

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. 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 group. 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 9.5.1.4.3, 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 group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 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, body temperature, and weight) and changes from baseline will be presented by day and time after dosing and treatment for both OSA and COPD cohorts.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at visits specified in the Schedule of Assessments table (Table 4).

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable

9.7.1.9 Other Analyses

Not applicable

9.7.2 Determination of Sample Size

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 less than 5.

Table 6 Estimation of Sample Size (OSA and COPD Cohorts)

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

AHI = apnea hypopnea index

COPD Cohort:

A 2% decrease in mean SpO2 during TST is considered a clinically meaningful change. For the primary hypothesis (mean SpO2 during TST on Day 8), assuming a true within subject variance of 1.07% for mean SpO2, a total of 30 subjects completing the crossover study, and significance level alpha 0.05, there is 0.95 probability that the lower bound of the 90% confidence interval for the true mean difference in mean SpO2 (LEM- placebo) on Day 8 would be greater than 2 percent points, if the true difference is 1 percent point. The true difference could be as low as 1.23% and the study still would have had 80% power to support the hypothesis.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

American Academy of Sleep Medicine. International classification of sleep disorders, 3rd edition. Darien, IL: American Academy of Sleep Medicine, 2014.

Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. Journal of Clinical Sleep Medicine. 2009;5(3):263-76.

Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep. 1995;18:425–32.

Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA. 1989;262:1479–84.

Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29(3):381–401

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease website. https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf. [updated December 2019. accessed 17 Dec 2019].

Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. Chest. 2001;120:1923–9.

Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. Sleep Breath. 2007;11(3):159–64.

Kryger M, Roth T, Wang-Weigand S, Zhang J. The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. Sleep Breath. 2009;13(1):79-84.

Lee YJ, Kim JW, Lee Y-U G, Jeong DU. Sleep EEG Characteristics in Young and Elderly Patients with Obstructive Sleep Apnea Syndrome. Psychiatry Investig. 2016;13(2):217-21.

Mitterling M, Högl B, Schönwald SV, Hackner H, Gabelia D, M, Birgit Frauscher B. Sleep and Respiration in 100 Healthy Caucasian Sleepers—A Polysomnographic Study According to American Academy of Sleep Medicine Standards. Sleep. 2015;38(6):867-75.

Piper AJ, Yee BJ. Hypoventilation syndromes. Compr Physiol. 2014; 4(4):1639-76

Rosenberg R, Roach JM, Scharf M, Amato DA. A pilot study evaluating acute use of eszopiclone in patients with mild to moderate obstructive sleep apnea syndrome. Sleep Med. 2007;8(5):464–70.

Sun H, Palcza J, Rosenberg R, Kryger M, Siringhaus T, Rowe J, et al. Effects of suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with chronic obstructive pulmonary disease. Respir med. 2015;109(3), 416-26.

Sun H, Palcza J, Card D, Gipson A, Rosenberg R, Kryger M, et al. Effects of suvorexant, an orexin receptor antagonist, on respiration during sleep in patients with obstructive sleep apnea. J Clin Sleep Med. 2016;12(1):9–17.

Vroegop AV, Smithuis JW, Benoist LBL, Vanderveken OM, de Vries N. CPAP washout prior to reevaluation polysomnography: a sleep surgeon's perspective. Sleep Breath. 2015 19(2):433–9.

C-SSRS Reference

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

GOLD 2019

https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf

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 health or 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 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 sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB 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, ECGs, rhythm strips, EEGs, polysomnograms, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- 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
- 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 correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

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

11.5 Identification of Source Data

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

The data collected by electronic Patient-Reported Outcome are also considered as source data.

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 for US sites). 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 15 years following the completion of the study.

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 CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

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/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 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 and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

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

11.11 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 – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
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×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
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
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	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; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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 without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), 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 5.0. Published: January 5, 2018.

Appendix 2 GOLD Recommendations for Performing Spirometry

Preparation

- Spirometers need calibration on a regular basis
- Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it
- The supervisor of the test needs training in optimal technique and quality performance
- Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management

Bronchodilation

- Possible dosage protocols are 400 mcg short acting beta agonist, 160 mcg short acting anticholinergic, or the two combined. Forced Expiratory Volume in 1 Second (FEV_1) should be measured 10 to 15 minutes after short acting β2 agonist is given, or 30 to 45 minutes after a short acting anticholinergic or a combination of both classes of drugs

Performance

- Spirometry should be performed using techniques that meet published standard
- The expiratory volume/time traces should be smooth and free from irregularities. The pause between inspiration and expiration should be <1 second
- The recording should go on long enough for a volume of plateau to be reached, which may take more than 15 seconds in severe disease
- Both forced vital capacity (FVC) and FEV1 should be the largest value obtained from any of 3 technically satisfactory curve and the FVC and FEV1 values in these 3 curves should vary by no more than 5% or 150 mL, whichever is greater
- The FEV_1 and FVC ratio should be taken from technically acceptable curve with the largest sum of FVC and FEV_1

Evaluation

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race
- The presence of postbronchodilator $FEV_1/FVC<0.70$ confirms the presence of airflow limitation

Appendix 3 Pharmacodynamic, and Other Biomarker Research

Objective

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic (PD), and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development

Collection of the PD, and other biomarker samples will be bound by the sample principles and processes outlined in the instructions manual / laboratory manual and the informed consent for the study. Sample collection for PD, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-113

Study Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Subjects With Moderate to Severe Obstructive Sleep Apnea and Adult and Elderly Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease

Investigational Product Name: E2006/lemborexant

IND Number: 111871

SIGNATURES

Authors:

PPD PPD PPD PPD PPD

Date

Eisai, Inc

PPD PPD PPD

Date

Eisai Inc.

PPD PPD PPD PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-113
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Subjects With Moderate to Severe Obstructive Sleep Apnea and Adult and Elderly Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease
Investigational Product Name:	E2006/lemborexant
IND Number:	111871

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

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date