Revision History

Previous Version: V5.0 (per Amendment 04)
Current Version: V6.0 (per Amendment 05)
Date of Revisions: 28 Jun 2022

Change	Rationale	Affected Section(s)
Added conditional permission to use local laboratories for clinical laboratory tests instead of the central laboratory only when the central laboratory cannot be used due to an unavoidable reason (eg, lockdown).	To monitor the subject's safety properly even in the case where the central laboratory cannot be used.	• Section 9.5.1.5.3

Previous Version: V4.0 (per Amendment 03) **Current Version: V5.0 (per Amendment 04)** **Date of Revisions: 17 Sep 2020**		
Change	**Rationale**	**Affected Section(s)**
Added to evaluate Insomnia Severity Index (ISI) total number in Secondary Objective	To evaluate insomnia severity	• Synopsis–Objectives • Synopsis–Statistical Methods • Section 8.1 • Section 9.7.1
Added time window for TEAEs	For clarification	• Section 9.7.1.8.2
Revised date of birth to date of birth (or age) in demographic information	For clarification	• Section 9.5.1.1

Previous Version: V3.0 (per Amendment 02) **Current Version: V4.0 (per Amendment 03)** **Date of Revisions: 18 Jun 2020**		
Change	**Rationale**	**Affected Section(s)**
Add one annotation about adult age in Taiwan in Inclusion Criteria	To meet the requirement of Taiwan authority	• Synopsis–Inclusion Criteria • Section 9.1 • Section 9.3.1
Removed "child-resistant" in investigational products	Tablets will be packaged in regular blister cards.	• Section 9.3.2
Revised volume of sample collection	For clarification	• Table 2
Removed the number of subjects (percentage)/events with TEAEs of cataplexy and related events from Safety Analysis Set	Per the deletion of Adjudication Committee	• Section 9.7.1.8.2
The medical monitor assigned for this study has been changed.	Administrative change	• Signature page

Previous Version: V2.0 (per Amendment 01) **Current Version: V3.0 (per Amendment 02)** **Date of Revisions: 12 Feb 2020**		
Change	**Rationale**	**Affected Section(s)**
Added moderate hepatic impairment in Exclusion Criteria (#7)	Per the comments from FDA and PMDA.	• Synopsis–Exclusion Criteria • Section 9.3.2
Removed alcohol consumption in electronic sleep diary	The alcohol consumption will only be self-reported by subjects	• Synopsis-Assessments
Added Serum pregnancy test (β-hCG) and Urine pregnancy test in Table 3	For clarity.	• Table 3
Corrected a typo in Section 9.5.5	For clarity.	• Section 9.5.2.1

Previous Version: V1.0 (original protocol)
Current Version: V2.0 (per Amendment 01)
Date of Revisions: 11 Sep 2019

Change	Rationale	Affected Section(s)
Revised approximate number of sites from 20 to 30.	To facilitate study enrollment.	• Synopsis–Sites • Section 6
Changed two study doses (lemborexant 5 mg, 10 mg) to one study dose (lemborexant 10 mg).	See. Section 9.4.4.	• Synopsis–Objectives • Synopsis–Study Design • Synopsis–Study Treatments • Section 9.1 • Section 9.2 • Section 9.4.4
Primary objective, changed from sSOL by sleep diary to LPS by PSG.	To incorporate feedback from regulatory China authority.	• Synopsis–Objectives • Section 8.1
Revised secondary objectives and exploratory objectives. Added change from baseline in BDI-II and BAI as exploratory objectives.	Per study objectives change and to explore the effects of treatment on BDI-II and BAI.	• Synopsis–Objectives • Section 8.3
Revised total number of expected screened subjects from 1000 to 700.	To align with the revised study design and to reflect current screen failure rate.	• Synopsis–Number of Subjects • Section 9.3
Added inclusion criteria (#7 and #9) and exclusion criteria (#14) relating PSG.	To align with the revised primary objective (LPS by PSG).	• Synopsis–Inclusion Criteria • Synopsis–Exclusion Criteria • Section 9.3.1 • Section 9.3.2
Deleted Adjudication Committee.	This committee is not required for China.	• Synopsis–Study Design • Section 9.2
Added PSG in assessment.	To align with the revised primary objective.	• Section 9.5.2.1
Revised statistical methods.	To align with revised primary objective, revised objectives, and one study dose.	• Synopsis–Statistical Methods • Section 9.7.1
Revised sample size rationale.	To align with revised primary objective, revised objectives, and one study dose.	• Synopsis–Sample Size Rationale • Section 9.7.2
Added updated information.	Add updated data of Study 303 and regulation.	• Section 7.1 • Section 7.2
Updated retention period	Per requirement of sponsor's policy.	• Section 11.6
Revised the detailed Inclusion/Exclusion Criteria Schedule.	For clarity.	• Appendix 2

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2006-J086-311
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 JP
Investigational Product Name:	E2006/lemborexant
Indication:	Insomnia
Phase:	3
Approval Date:	V1.0 02 Aug 2018 (original protocol) V2.0 11 Sep 2019 (per Amendment 01) V3.0 12 Feb 2020 (per Amendment 02) V4.0 18 Jun 2020 (per Amendment 03) V5.0 17 Sep 2020 (per Amendment 04) V6.0 28 Jun 2022 (per Amendment 05)
GCP Statement:	This study is to be performed in full compliance with China Good Clinical Practice (C-GCP) and all applicable 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, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder

Investigators

TBD

Sites

Up to 30 sites in China mainland and Taiwan

Study Period and Phase of Development

24 months

Phase 3

Objectives

Primary Objective (revised per Amendment 01)

- To confirm using polysomnography (PSG) that lemborexant 10 mg (LEM10) is superior to placebo (PBO) on objective sleep onset as assessed by latency to persistent sleep (LPS) during the last 2 nights of 1 month of treatment in subjects with insomnia disorder

Secondary Objectives (revised per Amendment 04)

- To evaluate LEM10 compared to PBO on sleep efficiency as assessed by objective sleep efficiency (SE) during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep maintenance as assessed by objective wake after sleep onset (WASO) during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep maintenance as assessed by subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), subjective wake after sleep onset (sWASO) over the last 7 nights of 1 month of treatment
- To evaluate the efficacy of LEM10 compared to PBO on sleep (LPS, WASO, SE) as measured by PSG during the first 2 nights of treatment
- To evaluate the safety and tolerability of lemborexant
- To evaluate the effect of lemborexant compared to PBO on insomnia severity and daytime functioning, as assessed by the Insomnia Severity Index (ISI)
- To evaluate rebound insomnia following completion of treatment with lemborexant
- To evaluate morning residual sleepiness during treatment and following completion of treatment with lemborexant

Exploratory Objectives (revised per Amendment 01)

- To explore the effects of LEM10 and PBO on subjective quality of sleep
- To evaluate the effects of LEM10 and PBO on sleep architecture
- To explore the effects of LEM10 and PBO on Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI)
- To summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10

Study Design

E2006-J086-311 is a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of lemborexant 10 mg for 30 nights in Chinese subjects (age 18 years or older) who have insomnia disorder. (revised per Amendment 01)

The study will have 2 phases: the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects will be treated for 30 nights, and a minimum 14-day Follow-Up Period before an End of Study (EOS) Visit.

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, weight, height (once at Visit 1), clinical hematology and chemistry analysis and urinalysis. At each visit from Screening to the EOS Visit, subjects will also undergo a urine drug screen.

Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further, that the subject complains of difficulties with sleep onset, sleep maintenance and/or early morning awakening. Screening assessments will include the ISI, as well as the BDI-II and BAI, STOPBang and International Restless Legs Scale (IRLS), collectively called the Sleep Disorders Screening Battery (SDSB).

All eligible subjects will be provided with an electronic device on which they will complete the sleep diary. Subjects will be trained in the use of this device. Site staff will instruct subjects to complete the diary each morning within 1 hour after morning wake time and will emphasize the importance of doing so. The sleep diary entries will be reviewed by site staff at least weekly throughout the study to ensure subject compliance with completion of the sleep diary and to ensure that study restrictions are met pertaining to duration of time spent in bed. Subjects will also be reminded of study restrictions pertaining to timing of meals and caffeine/alcohol use.

After subjects have completed the sleep diary on at least 7 consecutive mornings, provided that the sleep diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the second Screening Visit (Visit 2a). (Subjects who are not eligible based on sleep diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day –18 and Day –12. On this and all nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. After check-in has been completed, subjects will then undergo an 8-hour PSG recording, to start at the median habitual bedtime (MHB) as calculated from the sleep diary entries. The PSG recording will include channels in the electrode montage to screen for symptoms of sleep apnea and periodic limb movement disorder (PLMD). The PSG will be reviewed for inclusion criteria related to the presence of insomnia and absence of symptoms of sleep apnea and/or PLMD. Subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test. (revised per Amendment 01)

Run-in Period

The Run-in Period will begin when eligible subjects are dispensed PBO tablets and will continue until the Baseline Period on Day 1. During the Run-in Period, all subjects will take PBO each night approximately 5 minutes before bedtime (defined as the time the subject intends to try to fall asleep). They will be reminded that they must remain in bed for at least 7 hours each night and maintain a regular bedtime and waketime throughout the study, according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals, and use of caffeine and alcohol.

When subjects have completed the sleep diary on at least 7 consecutive mornings during the Run-in Period, the diary will be reviewed for continued eligibility. Subjects who are still eligible will return to the clinic for the first of 2 consecutive nights on which PSG will be recorded. The first of these 2 nights must be between Day –10 and Day –4. In the evening, before the PSG recording, the safety assessments will be conducted. Study personnel will administer study drug to subjects approximately 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second Screening Visit. Subjects will undergo an 8-hour PSG. The next morning, subjects will complete the sleep diary. The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that it is safe for them to do so. Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects approximately 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will complete the sleep diary. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic after the investigator determines that it is safe for them to do so. Subjects will continue to take study drug at home approximately 5 minutes before bedtime and they will continue to complete the sleep diary each morning within 1 hour after morning wake time. They will again be reminded that they must remain in bed for at least 7 hours each night, maintain a regular bedtime throughout the study, and follow study restrictions with regard to timing of meals and use of caffeine and alcohol. Urine drug test will be performed as described in Section 9.5.2. (revised per Amendment 01)

Baseline Period

On Day 1, the Run-in Period will end and the Baseline Period will begin. Subjects will return to the clinic for this visit, and the ISI will be administered. Blood and urine samples will be collected for routine safety assessments, an ECG will be performed, and vital signs and weight will be assessed. In addition, subjects should undergo a urine drug test. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period. (revised per Amendment 01)

Treatment Period

The Treatment Period will begin on Day 1 and will continue until Day 31. Subjects will be randomized in a double-blind manner, to receive LEM10, or PBO. (revised per Amendment 01)

On the evening of Day1, approximately 5 minutes before the subject's MHB, study drug will be administered and an 8-hour overnight PSG will be initiated. At completion of the PSG recording the following morning (Day 2), subjects will complete the sleep diary. They may leave the clinic after the investigator determines that is safe for them to do so. On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB, followed by an overnight PSG. On the morning of Day 3, a PK sample will be obtained and subjects will complete the sleep diary. Subjects may then leave the clinic after the investigator determines that it is safe for them to do so. Study drug will be dispensed and subjects will be provided with instructions to continue completing the sleep diary each morning within 1 hour of waketime and taking study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period. On Day 29, subjects will return to the clinic. Study drug will be administered approximately 5 minutes before the subject's MHB, followed immediately by a PSG. On the morning of Day 30, subjects will complete the sleep diary, and may leave the clinic after the investigator determines that it is safe for them to do so. On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, a PK sample will be obtained. Subjects will complete the sleep diary. Then the ISI, BDI-II and BAI will be administered. Blood and urine samples will be collected for routine safety assessments. An ECG will be performed, and vital signs and weight will be assessed. Then, after the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic. Urine drug test will be performed as described in Section 9.5.2. (revised per Amendment 01)

Follow-Up Period and End of Study (EOS) Visit

The Follow-Up Period will begin when the subjects leave the clinic at the end of the Treatment Period. Subjects will cease to take study drug but will continue to complete the sleep diary each morning until the EOS Visit.

At least 14 days but no more than 18 days after completion of the Treatment Period, subjects will return to the clinic for the EOS Visit. At the EOS Visit, in addition to standard safety assessments, a urine drug test will be

conducted, and sleep diaries will be collected. After the EOS Visit, subjects' participation in the study will be finished.

Premature Discontinuation of Study Drug

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug (preferably within 7 days), to complete the Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and all AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study informed consent form (ICF) through the last visit. All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

Additional Study Information

The estimated duration for each subject on study is anticipated to be a maximum of 89 days (12.7 weeks) consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-Up Period and EOS Visit maximum of 54 days. A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study.

Number of Subjects

For overall subjects, approximately a total of 700 subjects will be screened to provide approximately 188 overall randomized subjects. Subjects will be randomized to one of the following treatment arms: LEM10, PBO, in an approximate 1:1 ratio. (revised per Amendment 01)

Inclusion Criteria

1. Chinese male or female, age 18 years or older, at the time of informed consent (in Taiwan only subjects with age 20 years or older are eligible) (revised per Amendment 03)
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥ 3 times per week
   - Duration of complaint ≥ 3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of sSOL ≥30 minutes on at least 3 nights per week in the previous 4 weeks AND/OR sWASO ≥60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At second Screening Visit (Visit 2a) and Run-in Visit (Visit 3a): Sleep diary confirms regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 on at least 5 of the final 7 nights and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00 on at least 5 of the final 7 nights (revised per Amendment 01)
6. At Screening and Baseline: ISI score ≥15 (revised per Amendment 01)
7. Confirmation of current insomnia symptoms, as determined from responses on the sleep diary on the 7 most recent mornings before the first PSG during Screening Period (Visit 2a) and Run-in visit (Visit 3a), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 01)
8. At the second Screening Visit (Visit 2a) and the Run-in visit (Visit 3a): Confirmation of sufficient duration of time spent in bed, as determined from responses on the sleep diary on the 7 most recent mornings before the Visit, such that there are no more than 2 nights with time spent in bed duration <7 hours or >10 hours (revised per Amendment 01)
9. During the Run-in Period, objective (PSG) evidence of insomnia as follows:
   a. LPS average ≥30 minutes on the 2 consecutive baseline PSGs, with neither night <20 minutes and/or

b. WASO average ≥60 minutes on the two consecutive baseline PSGs, with neither night <45 minutes (revised per Amendment 01)

10. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
11. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

Exclusion Criteria

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
2. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system (IUS)
     - a contraceptive implant
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
3. Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
4. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolonged the QTcF interval.
5. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening
6. Any suicidal behavior in the past 10 years
7. Evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal; moderate and severe hepatic impairment; renal including severe renal impairment; neurological including myasthenia gravis; psychiatric disease; or malignancy within the past 5 years other than adequately treated basal cell carcinoma) or chronic pain that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. (revised per Amendment 02) Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded
8. Hypersensitivity to lemborexant or to their excipients
9. Scheduled for surgery during the study

10. Known to be human immunodeficiency virus (HIV) positive
11. Active viral hepatitis (B or C) as demonstrated by positive serology
12. History of drug or alcohol dependency or abuse within approximately the last 2 years
13. A current diagnosis of sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
    - STOPBang score ≥5
    - IRLS ≥16
14. Apnea-Hypopnea Index >15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second Screening Visit (revised per Amendment 01)
15. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy
16. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping)
17. For subjects who underwent diagnostic PSG within 1 year before informed consent:
    - Age 18 to 64 years: Apnea Hypopnea Index ≥10, or Periodic Limb Movements with Arousal Index ≥10
    - Age ≥65 years: Apnea Hypopnea Index >15, or Periodic Limb Movements with Arousal Index >15
18. BDI-II score >19 at Screening
19. BAI score >15 at Screening
20. Habitually naps during the day more than 3 times per week
21. Excessive caffeine use that in the opinion of the investigator contributes to the subject's insomnia, or habitually consumes caffeine containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and ≥5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation. To be exclusionary, those symptoms must cause distress or impairment in social, occupational and other forms of functioning, and not be associated with other substance, mental disorder or medical condition
22. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3 hours before bedtime for the duration of his/her participation in the study
23. Excluding comorbid nocturia that is causing or exacerbating the insomnia
24. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period). (A list of prohibited concomitant medications is presented in Appendix 3 of protocol)
25. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period)
26. Failed treatment with dual orexin receptor antagonist drugs (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator (revised per Amendment 01)

27. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study (China mainland will be considered as 1 time zone) (revised per Amendment 01)
28. A positive drug test at Screening, Run-in, or Baseline, or unwilling to refrain from use of recreational drugs during the study
29. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5× the half-life, whichever is longer preceding informed consent
30. Previously participated in any clinical trial of lemborexant

Study Treatments

Test drug:

Lemborexant 10 mg, or lemborexant-matched PBO will be taken orally in tablet form each night for 30 consecutive nights approximately 5 minutes before the time the subject intends to try to sleep (revised per Amendment 01)

Run-in Period

All subjects will receive 1 lemborexant matched PBO in a single blind manner during the Run-in Period approximately 5 minutes before the time the subject intends to try to sleep. (revised per Amendment 01)

Treatment Period

All subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized: (revised per Amendment 01)

- LEM10: 1 lemborexant 10 mg tablet
- PBO: 1 placebo tablet matched to lemborexant 10 mg

Duration of Treatment

A maximum of approximately 7.5 weeks: Up to 17 days of PBO during the Run-in Period, up to 35 days of randomized treatment.

Concomitant Drug/Therapy

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. (revised per Amendment 01)

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcohol containing drinks on any given day while in the study, and will be instructed not to consume any alcohol within 3 hours before bedtime. A drink will be defined as 285 mL of beer, 150 mL of wine, or 25 mL of liquor. Subjects must not consume any alcohol on days when they are scheduled for a PSG recording. (revised per Amendment 01)

Prohibited medications (presented in Appendix 3 of protocol) should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period).

Prohibited medications include moderate and strong cytochrome P450 (CYP3A) inhibitors and all CYP3A inducers. (revised per Amendment 01) Prohibited therapies also include: any treatment for insomnia disorder, including any drugs or nonpharmacological treatment such as cognitive behavioral therapy; medications that are used for the purpose of inducing sleep (hypnotics) or inducing wakefulness (stimulants; except caffeine; see above) and medications that have known sedating effects or alerting effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications but in the opinion of the investigator causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

If a subject starts any prohibited medication or therapy during the study, 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 moderate and strong CYP3A inhibitors will not be permitted at any time for any duration during the study. (revised per Amendment 01)

Assessments

Screening Assessments (administered only at first Screening Visit)

SDSB

The SDSB will include the:

- StopBANG: a list of eight questions to be answered Yes or No, which screens subjects for obstructive sleep apnea
- IRLS: a subjective scale comprising ten questions, which measures severity of symptoms of restless legs syndrome

Efficacy Assessments

PSG (revised per Amendment 01)

Each PSG recording will include an electrode montage with electroencephalography (EEG), electromyography (EMG), electrooculography, and ECG channels, for scoring of sleep parameters and sleep architecture via standard sleep scoring criteria. In addition, the first PSG will include channels for assessment of symptoms of sleep apnea and periodic limb movement disorder.

Trained PSG scorers will score PSG records in 30-second epochs according to standard criteria. The PSG at the second Screening Visit will be used only to calculate the Apnea-Hypopnea Index and the Periodic Limb Movements with Arousal Index for evaluation of eligibility criteria; sleep parameters and sleep architecture will not be evaluated from this PSG. The 2 PSGs obtained during the Run-in Period will be used to a) determine eligibility and b) derive baseline PSG parameters for those subjects who are randomized.

All PSG parameters will be obtained separately for each PSG recording and averaged across the pairs of consecutive PSG nights.

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per time in bed (TIB), calculated as total sleep time (TST)/interval from lights off until lights on
- WASO: minutes of wake from the onset of persistent sleep until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least one epoch of wake, after onset of persistent sleep, and including any terminal awakening)

Additional sleep architecture parameters will be also calculated from each PSG, including:

- Sleep onset latency: minutes from lights off to the first epoch of any stage of sleep (N1, N2, N3, rapid eye movement [REM])
- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening could not be interrupted by stage N1, but must have been interrupted by stage N2, N3, or REM
- Number of long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least 1 epoch of wake, after onset of persistent sleep, and including any terminal awakening)
- Percentage of stage wake and sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep

- Percentage of sleep stages per TST: NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of sleep (N1, N2, or N3) to first epoch of REM

Each of these PSG-derived variables, with the exceptions of SE, REM episode frequency and duration, mean REM/NREM cycle duration, and REM latency, will also be calculated by hour and by half of the 8-hour time interval in bed.

Electronic Sleep Diary

The sleep diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the study. Sleep diary entries may be maintained in paper format as a backup to the electronic sleep diary, if necessary. This sleep diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety. In addition, the sleep diary will include questions that relate to morning sleepiness.

Sleep Parameters:

- sSOL: estimated minutes from the time that the subject attempts to sleep until sleep onset
- sWASO: sum of estimated minutes of wake during the night after initial sleep onset until the time that the subject stopped trying to sleep for the night
- Subjective total sleep time (sTST): derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
- sSE: proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reported attempting to sleep until the time the subject stopped trying to sleep for the night, and time spent asleep derived from subjective time spent in bed minus sWASO

Sleep architecture parameters will be calculated as described above under assessments. (revised per Amendment 01)

Quality of Sleep and Morning Sleepiness

The sleep diary will be used to assess the subject's global perception of quality of sleep on the previous night with the following question: "How would you rate the quality of your sleep last night?" Subjects will rate the quality of their sleep on a scale from 1 to 9, with 1 being extremely poor and 9 being extremely good.

The sleep diary will be used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" Subjects will rate their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely sleepy and 9 being extremely alert.

Insomnia Severity Index

The ISI is a 7-item self-report questionnaire assessing the nature, severity and impact of insomnia. The dimensions evaluated are severity of: sleep onset, sleep maintenance, early-morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning, noticeability of the sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (from 0 =no problem to 4=very severe problem), yielding a total score from 0 to 28.

BDI-II (revised per Amendment 01)

The BDI-II is a 21-question multiple-choice self-report questionnaire that subjects will use to rate the presence, frequency, and severity of symptoms of depression using a 4-point Likert scale. Scores on the BDI-II range from 0 to 63, with higher scores indicating higher levels of depressive symptoms. Subjects with BDI-II scores >19 will be excluded from participation.

BAI (revised per Amendment 01)

The BAI is a 21-question multiple-choice self-report inventory that subjects will use to rate the presence, frequency, and severity of symptoms of anxiety using a 4-point Likert scale. Scores on the BAI range from 0 to 63, with higher scores indicating higher levels of anxiety symptoms. Subjects with scores on the BAI >15 will be excluded from participation.

Pharmacokinetic Assessments

A single blood sample for plasma concentrations of lemborexant and its metabolites M4, M9 and M10 will be taken at predefined visits. The time and date of the 2 most recent lemborexant doses administered before each sample will be documented.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, including after the last dose of study drug, and at the EOS, ET, and Unscheduled Visits.

Bioanalytical Methods

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

Statistical Methods

All statistical tests will be based on the 5% level of significance (2-sided).

Study Endpoints

Primary Endpoint (revised per Amendment 01)

- Change from baseline of objective LPS during the last 2 nights of 1 month of treatment of LEM10 compared to PBO

Secondary Endpoints (revised per Amendment 04)

- Change from baseline of objective SE during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline objective WASO during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSOL during the last 7 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSE during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of sWASO during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of PSG parameters (LPS, SE, WASO) over the first 2 nights of 30 nights of LEM10 compared to PBO
- Safety and tolerability of lemborexant
- Change from Study Baseline in insomnia severity and daytime functioning, assessed as the total score and from the 4 items related to daily function on the ISI after 1 month of treatment with LEM10 compared to PBO
- Rebound insomnia endpoints as assessed from the sleep diary during the Follow-Up Period
- Morning residual sleepiness during treatment and following completion of treatment

Exploratory Endpoints (revised per Amendment 01)

- Subjective quality of sleep
- Sleep architecture
- Effects on Beck Depression Inventory–II and Beck Anxiety Inventory
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

Analysis Sets

- The Safety Analysis Set is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement.

- The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding will be specified in the Statistical Analysis Plan (SAP).
- The PK Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least one quantifiable plasma concentration of lemborexant or its metabolites, with adequately documented dosing history.

Efficacy Analyses

The efficacy analyses will be performed on the FAS except per protocol analysis will be performed on the PP. (revised per Amendment 01)

Definitions of Baseline

Baseline data are captured during the Run-in and Baseline Period.

Analysis for the Primary Endpoint (revised per Amendment 01)

Null Hypothesis: For objective LPS, no difference exists in the mean change from Study Baseline to the last 2 nights of Month 1 of treatment with LEM10 compared with PBO.

Alternative Hypothesis: For objective LPS, a difference exists in the mean change from Study Baseline to the last 2 nights of Month 1 for LEM10 compared with PBO.

The objective LPS change from Baseline (the mean of Days 1 and 2, and the mean of Day 29 and 30) will be analyzed using the mixed effect model repeated measurement analysis (MMRM) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), site, age group (<65 years old; ≥65 years old), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. Factor "Site" will be defined in the SAP before database lock. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputations (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV-subjects who completed primary efficacy assessments without missing values). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The *P*-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided.

Subgroup analyses and additional sensitivity analysis will be performed as appropriate.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described above will be repeated on subjects who completed all efficacy assessments and have no missing values.
- As-treated analysis: The same primary efficacy analyses (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.
- MMRM analysis assuming missing at random (MAR): The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are MAR.
- MI Imputation assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows)

Study days where results are available	**1**	**2**	**29**	**30**
Pattern 1	x	x	x	x
Pattern 2	x	x	x	–
Pattern 3	x	x	–	–
Pattern 4	x	–	–	–

x: result present; – : result missing

Secondary Efficacy Analysis (revised per Amendment 04)

The other efficacy endpoints (change from Baseline of the following for LEM10 compared to PBO; mean objective SE, mean objective WASO, mean sSOL, mean sSE, and mean sWASO at the first 7 nights and last 7 nights of treatment; ISI total number and total score of 4 items of daytime functioning after 1 month of treatment) will be analyzed using the MMRM, assuming the missing values are MAR. The sSOL will be implemented on the log-transformation.

Subgroup analyses will be defined SAP in detail.

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep diary data from the Follow-Up Period will be compared to sleep diary data from the Screening Period to assess whether subjects experience rebound insomnia. To assess rebound insomnia, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the first 3 nights and each of the 2 weeks of the Follow-Up Period the proportion of subjects whose corresponding value for sSOL or sWASO exceeds the corresponding Screening Period value by 5 minutes will be summarized by treatment group and compared to PBO. The percentage of 'rebounders' between LEM10 and PBO group will be analyzed using a chi-square test. To assess statistical significance using the continuous data, the data will be analyzed using analysis of covariance (ANCOVA). The LS mean of each of the first 3 nights and each week of the Follow-Up Period will be compared to the Screening Period between LEM10 and PBO. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-Up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen will be considered to evaluate whether clinically meaningful rebound insomnia is present.

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the sleep diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-Up Period will be analyzed using MMRM assuming MAR.

Exploratory Efficacy and Pharmacodynamic Analyses

The change from Baseline for the mean score of the quality of sleep item on the sleep diary will be analyzed, to consider the subjective quality of sleep, using MMRM, assuming MAR for the mean of the first 7 days after 1 month of treatment. The change from Baseline (at Screening) for BDI-II and BAI will be analyzed using ANCOVA including treatment and Baseline. Other efficacy measures will be tabulated, and may be plotted, but will not be statistically analyzed.

Pharmacokinetic Analysis

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

Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs and weight, along with change from baseline in laboratory safety test variables, ECGs, and vital sign and weight measurements, will be summarized by treatment group using descriptive statistics.

Other Analyses

Secondary and exploratory endpoints may be additionally presented graphically or analyzed by modeling methods if warranted.

Details of all of analysis will be specified in the SAP.

Interim Analyses (revised per Amendment 01)

This is a fixed design. There is no interim analysis for efficacy and no alpha spending before final analysis. However a blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, may be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment.

Sample Size Rationale (revised per Amendment 01)

The sample size was considered based on LPS for each comparison between Study 201(E2006-G000-201) and Study 304 (E2006-G000-304). For LEM10 on Days 29 and 30, we assume the effect size that mean difference divided by common standard deviation as –0.411 under logarithm transformation. Therefore, to detect a difference in LPS comparing LEM10 with PBO, at least 94 subjects per group (total 188) will be needed for a 0.05 α-level, 2-sided test and more than 80% power based on above assumption.

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
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0\text{-inf})}$	area under the concentration-time curve extrapolated from zero time to infinite time
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory–II
BMI	body mass index
BP	blood pressure
CCMV	complete case missing value
CI	confidence interval
CMQ	customized MedDRA queries
CPAP	continuous positive airway pressure
C_{max}	maximum observed concentration
CPMP	Committee for Proprietary Medicinal Products,
CRA	clinical research associate
CRO	Contract Research Organization
CTA	Clinical Trial Authorisation
CYP3A	cytochrome P450
DORA	dual orexin receptor antagonist
DurLongAw	Mean duration of long awakenings
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalography
EMG	electromyography
EOS	end of study
ET	early termination
FAS	Full Analysis Set

Abbreviation	Term
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
IxRS	an interactive voice and web response system
KSS	Karolinska Sleepiness Scale
LEM5	lemborexant, 5-mg dose
LEM10	lemborexant, 10-mg dose
LNH	low-normal-high
LPS	latency to persistent sleep
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MHB	median habitual bedtime
MI	multiple imputations
MMRM	mixed effect model repeated measurement
M-MSLT	modified multiple sleep onset latency test
MNAR	missing not at random
NDA	New Drug Application
NMPA	National Medical Products Administration
NREM	non-REM sleep
PBO	placebo
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLMD	periodic limb movement disorder
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per Protocol

Abbreviation	Term
PSG	polysomnography
PT	preferred term
QTcF	QT interval corrected for heart rate by Fridericia's formula
REM	rapid eye movement (sleep stage)
SAE	serious adverse event
SAP	statistical analysis plan
SDSB	Sleep Disorders Screening Battery
SE	objective sleep efficiency
SOC	system organ class
SOP	standard operating procedure
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
TEAE	treatment-emergent adverse event
TIB	time in bed
TST	total sleep time
WASO	objective wake after sleep onset
WASO2H	wake after sleep onset in the second half of the night

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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

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

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- A waiver from the [IRB(s)/IEC(s)] will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or appropriate 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 as well as contact information (phone number(s) of investigational site and name(s) of contact person). 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/IEC-approved ICF must be prepared in accordance with C-GCP, 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.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) up to 30 sites in China mainland and Taiwan. (revised per Amendment 01)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO(s)) are listed in the Investigator Study File or Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

Insomnia is a sleep disorder characterized by difficulties with sleep onset and/or sleep maintenance, which is the most prominent among numerous sleep disorders known today. In industrialized nations, approximately 30% of the population has symptoms and at least 6% meet diagnostic criteria for primary insomnia meriting treatment (Roth T, 2007). The percentages of subjects in China presenting with both night-time and daytime symptoms that meet the diagnostic criteria of DSM-IV, were 12.1% on average across 10 countries and 10.0% in China (Soldatos CR, et al., 2005). According to more recent research reported by the Chinese Sleep Research Society in 2014, 38.2% of Chinese people suffer from a sleep disorder, with insomnia one of the most frequent.

7.1.1 Current Therapeutics Options

Currently available pharmacological treatments used clinically in the world for insomnia include benzodiazepines, non-benzodiazepine GABA-releasing (GABAergics) agents, antidepressants, melatonin and melatonin agonists, antihistamines, etc. For National Medical Products Administration (NMPA) approved pharmacological treatments, there is no difference between approved dosages in China and globally approved dosages for insomnia drugs, for the most commonly used non-benzodiazepines: zolpidem (10 mg/day in both US and China); eszopiclone, (2 or 3 mg/day in both US and China). However, there has been increased awareness of the need for sleep-promoting agents with mechanisms of action different from GABA-A receptor positive-allosteric modulators. Orexin neuropeptides (orexin A and orexin B) have been recognized as critical upstream controllers of most wake-promoting neurotransmitters via 2 G protein coupled receptors, the OX1R and OX2R. Antagonists that block both OX1R and OX2R receptor are called dual orexin receptor antagonists (DORA). DORAs provide an alternative approach to treat insomnia disorder with better benefit/risk balance than those of other currently available medications. The only approved DORA is suvorexant, which was approved in US and Japan but not in China.

7.1.2 Lemborexant (E2006)

7.1.2.1 Mechanism of Action

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

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

7.1.2.2 Clinical Experience With Lemborexant

7.1.2.2.1 PHASE 1

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

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

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

E2006-A001-004 (Study 004): metabolism-based inducer/inhibitor study. This study provided data demonstrating (1) strong inhibitors of cytochrome P450 (CYP3A) lead to higher plasma concentrations of lemborexant; and (2) strong inducers of CYP3A lead to notably lower plasma concentrations of lemborexant. The study also demonstrated a weak effect of lemborexant on CYP2B6 activity and no effect on CYP3A activity.

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

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

E2006-A001-008 (Study 008): food effect study. This study demonstrated a mild food effect. The C_{max} was decreased by 23% and the area under the concentration-time curve from zero time extrapolated to infinite time ($AUC_{0\text{-}inf}$) was increased by 18% following consumption of a high fat meal.

E2006-A001-012 (Study 012): drug-drug interaction study. These study results demonstrated that: (1) coadministration of a moderate CYP3A inhibitor (fluconazole) showed a moderate interaction as demonstrated by a 1.63-fold increase in C_{max} and 4.2-fold increase in AUC of lemborexant; (2) coadministration of lemborexant had no statistically

significant effect on the PK of oral contraceptives (ethinyl estradiol and norethindrone), and these oral contraceptives did not alter the PK of lemborexant; and (3) concomitant administration of a gastric acid suppressant agent had a weak interaction with lemborexant as shown by a 27% decrease in C_{max} and no impact on AUC of lemborexant.

E2006-E044-106 (Study 106): Study 106 evaluated next-morning effects of lemborexant compared with PBO, with zopiclone included as a positive control, by measuring adult and elderly participants driving performance via an on-road driving test. The primary endpoint was to evaluate difference from PBO of standard deviation of lateral position (SDLP) during an on-road driving test on the mornings following the first and last dose of drug in each treatment period. Drug-PBO differences in SDLP >2.4 cm are considered to reflect clinically meaningful driving impairment. Lemborexant 2.5, 5 and 10 mg showed no statistically significant impairment of driving performance, as measured by mean changes in SDLP, after either single (Day 2) or multiple (Day 9) dose administration compared to PBO, meeting the study's primary endpoint. In contrast, zopiclone 7.5 mg significantly increased mean SDLP as compared to PBO. The upper bound of the 95 percent confidence intervals for the mean changes in SDLP were all below 2.4 cm for all three doses of lemborexant on Days 2 and 9, indicating that there was not clinically meaningful driving impairment. The upper bound of the 95 percent confidence intervals for the mean changes in SDLP for zopiclone was >2.4 cm on Days 2 and 9, demonstrating assay sensitivity.

E2006-A001-107 (Study 107): This Phase 1 study was conducted to evaluate the effects of the 5 and 10 mg doses on next-morning residual sleepiness in subjects with insomnia disorder. The study design was randomized, double-blind, and PBO-controlled with a 3-way crossover. Next morning residual sleepiness was measured on a modified multiple sleep onset latency test (M-MSLT). An active comparator, flurazepam 30 mg, was included to confirm assay sensitivity. Results showed that for neither 5 mg nor 10 mg was the lower bound of the 95% confidence interval (CI) of the treatment difference in change from baseline of average sleep onset latency on the M-MSLT more than 6 minutes, which was the prespecified criterion defining clinically meaningful next-morning residual sleepiness. That is, neither dose level of lemborexant resulted in a clinically meaningful reduction in average time to sleep onset in the morning hours, supporting the safety of these doses and their use in Phase 3 studies.

E2006-A001-108 (Study 108): Study 108 evaluated the effect of lemborexant on postural stability, auditory awakening threshold and cognitive performance in healthy volunteers age 55 years and older. Participants were administered a single dose of PBO, lemborexant 5 mg (LEM5), lemborexant 10 mg (LEM10), or zolpidem ER 6.25 mg, and had eight-hour polysomnograms at baseline and at each single-dose treatment. Body sway was assessed upon awakening participants after approximately four hours in bed. Study demonstrated that mean change from baseline in postural stability during middle of the night awakening is significantly and clinically meaningfully less after LEM5 and LEM10 than after zolpidem ER. The next morning, shortly after the end of eight hours in bed, unlike zolpidem ER, neither dose of lemborexant had statistically significant residual effects on this measure of postural stability as compared to PBO. This study also evaluated the effects of LEM5 and LEM10 on the auditory awakening threshold (AAT) at approximately four hours post-dose,

compared to zolpidem ER and PBO. Neither dose of lemborexant had a statistically significant difference relative to PBO or zolpidem ER on the ability to awaken to an external stimulus. There were no differences between PBO and LEM5 on measures of attention and memory, and subjects taking 10 mg performed less well than PBO in the middle of the night. No significant difference was found in Power of Attention and Quality of Memory between lemborexant treatments and PBO in the morning.

7.1.2.2.2 PHASE 2

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

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

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

7.1.2.2.3 PHASE 3

E2006-G000-304 (Study 304): Study 304 was a multicenter, randomized, double-blind, PBO-controlled, active comparator, parallel-group study of the efficacy and safety of lemborexant in patients 55 years and older with insomnia disorder, conducted in North America and Europe. Subjects were administered PBO or one of three treatment regimens (LEM5, LEM10, zolpidem ER 6.25 mg). The primary endpoint was change from baseline in LPS of both lemborexant doses compared to PBO, measured objectively by PSG. The key secondary endpoints included change from baseline in SE, and WASO for both lemborexant doses compared to PBO as well as WASO in the second half of the night (WASO2H) for both lemborexant doses compared to zolpidem ER, after 1 month of treatment, measured objectively by PSG. Study 304 achieved its primary and all of the key secondary objectives versus PBO and versus zolpidem ER. For additional efficacy endpoints as assessed by subjective sleep diary, both doses of lemborexant were statistically superior to PBO on sSOL sSE, sWASO, and sTST, over the first 7 nights and the last 7 nights of treatment.

E2006-G000-303 (Study 303): Study 303 was a multicenter, randomized, double-blind, PBO -controlled, parallel-group study of 2 dose levels of lemborexant in patients with insomnia disorder, conducted in North America, South America, Europe, Asia, and Oceania. Subjects were administered PBO or one of two treatment regimens (LEM5, LEM10). The primary endpoint was mean change from baseline in sSOL of both lemborexant doses compared to PBO, after 6 month of treatment, measured subjectively by sleep diary. The key secondary endpoints included mean change from baseline in sSE and sWASO for both lemborexant doses compared to PBO, after 6 month of treatment, measured subjectively by sleep diary. In Study 303, both doses of lemborexant demonstrated statistically significantly larger changes (positive outcome) from Study Baseline compared to PBO for both sleep onset and sleep maintenance variables after 6 months of treatment. (revised per Amendment 01)

Based on these data, a New Drug Application (NDA) for lemborexant was submitted to the US Food and Drug Administration (FDA) for the treatment of insomnia disorder in December 2018 and accepted for review in February 2019. Subsequently, NDA for lemborexant was submitted to the Japan Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of insomnia disorder in March 2019 and to Health Canada in August 2019. The data demonstrated efficacy of lemborexant 10 mg on objective and subjective measures of sleep onset and sleep maintenance. (revised per Amendment 01)

7.2 Study Rationale

Clinical studies of lemborexant has been conducted or are in the process of conducting with 16 Phase 1/Pharmacology studies and a Phase 2 dose range-finding study in insomnia disorder, sequentially confirming the safety and efficacy of lemborexant in healthy volunteers, patients with insomnia as well as some requisite special populations (Section 7.1.2.2.1). Lemborexant clinical development program included two multinational Phase 3 studies, Studies 303 and 304, which have been conducted overseas (Section 7.1.2.2.3). Study 304 demonstrated that short-term (1 month) treatment of lemborexant is effective on objective sleep latency and sleep maintenance assessed by PSG. Study 303 was designed to provide evidence of long-term efficacy of lemborexant on subjective sleep latency and sleep maintenance assessed by sleep diary.

In the original protocol (Version 1.0; 02 Aug 2018) of this Study 311, submitted with the Clinical Trial Authorisation (CTA), all sleep parameters were subjectively assessed by sleep diary, with no objective assessments by PSG. The CTA for the lemborexant program in China was filed with the Center for Drug Evaluation (CDE) in September 2018, and was approved in January 2019. The CDE recommended that Study 311 use the same primary and key secondary endpoints as the global Phase 3 study (Study 304), that are objectively assessment by PSG. (revised per Amendment 01)

As per CDE recommendation, Study 311 will be a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of the efficacy and safety of 1 dose level of lemborexant (10 mg) for 30 nights in Chinese subjects with insomnia. Similar to Study 304, all subjects will be assessed for objective sleep measures using PSG in order to demonstrate the statistical difference between LEM10 and PBO in LPS after 1 month of treatment.

Patient-reported (subjective) sleep measures will also be assessed using a sleep diary. (revised per Amendment 01)

The treatment period is 1 month. This treatment period meets the recommendation from the Guideline for the diagnosis and treatment of adult insomnia in China, which recommend treatment evaluation for 4 weeks. This short-term study should be sufficient for the China NDA because long-term data will be provided by Study 303.

Subjects will be Chinese male or female, age 18 years or older in order to evaluate patients of a broad age-range. There is no need to specify the number of elderly subjects in Study 311 as there are sufficient data on elderly patients from Study 303 and Study 304.

Subjects will be randomized to LEM10 or PBO treatment in an approximate 1:1 ratio. For the development of sleep-promoting drugs, because it is not able to exclude PBO effect in active drugs, a PBO-controlled trial is required for assay of efficacy and safety. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective (revised per Amendment 01)

To confirm using PSG that lemborexant LEM10 is superior to PBO on objective sleep onset as assessed by LPS during the last 2 nights of 1 month of treatment in subjects with insomnia disorder

8.2 Secondary Objectives (revised per Amendment 04)

The secondary objectives are:

- To evaluate LEM10 compared to PBO on sleep efficiency as assessed by SE during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep on sleep maintenance as assessed by WASO during the last 2 nights of treatment
- To evaluate LEM10 compared to PBO on sleep maintenance as assessed by sSOL, sSE, sWASO over the last 7 nights of 1 month of treatment
- To evaluate the efficacy of LEM10 compared to PBO on sleep (LPS, WASO, SE) as measured by PSG during the first 2 nights of treatment
- To evaluate the safety and tolerability of lemborexant
- To evaluate the effect of lemborexant compared to PBO on insomnia severity and daytime functioning, as assessed by the Insomnia Severity Index (ISI)
- To evaluate rebound insomnia following completion of treatment with lemborexant

- To evaluate morning residual sleepiness during treatment and following completion of treatment with lemborexant

8.3 Exploratory Objectives (revised per Amendment 01)

The exploratory objectives are:

- To explore the effects of LEM10 and PBO on subjective quality of sleep
- To evaluate the effects of LEM10 and PBO on sleep architecture
- To explore the effects of LEM10 and PBO on Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI)
- To summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-J086-311 is a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of LEM10 for 30 nights in Chinese subjects (age 18 years or older, only in Taiwan age 20 years and older) who have insomnia disorder. (revised per Amendment 03)

The study will have 2 phases: the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects will be treated for 30 nights, and a minimum 14-day Follow-Up Period before an End of Study (EOS) Visit.

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead ECGs, vital signs, weight, height (once at Visit 1), clinical hematology and chemistry analysis and urinalysis. At each visit from Screening to the EOS Visit, subjects will also undergo a urine drug screen.

Estimates for End of study are as follows:

- The end of the study will be the date of the last study visit for the last subject in the study
- The estimated duration for each subject on study is anticipated to be a maximum of 89 days (12.7 weeks) consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-Up Period and EOS Visit maximum of 54 days. A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study.

An overview of the study design is presented in Figure 1.

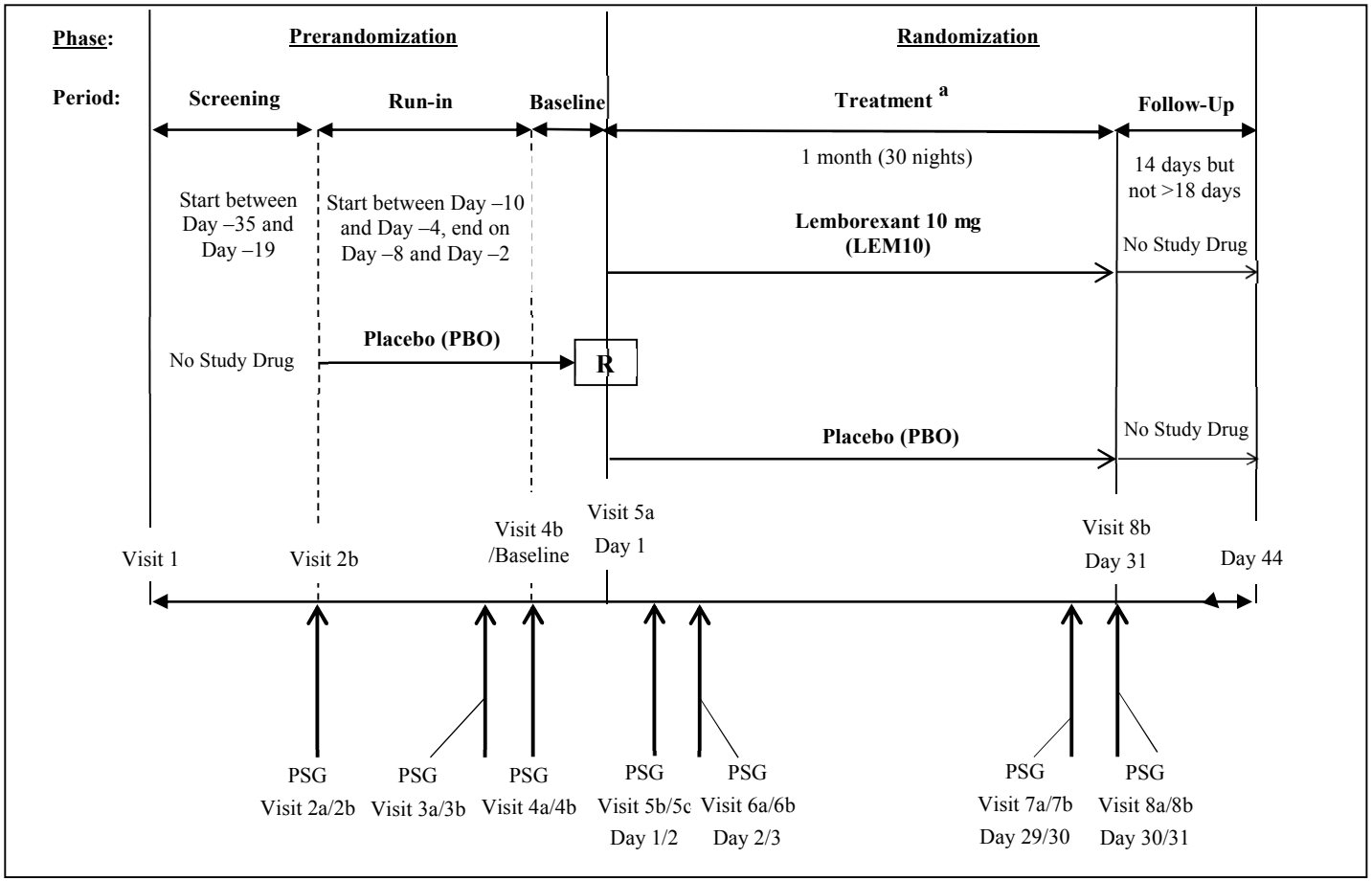

Figure 1 Schematic Diagram of E2006-J086-311 Study Design

PSG = polysomnography, R = randomization.

a: The first dose of active study drug will be administered at Visit 5b. The last dose of active study drug will be administered at Visit 8a.

9.1.1 Prerandomization Phase

9.1.1.1 Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further, that the subject complains of difficulties with sleep onset, sleep maintenance and/or early morning awakening. Screening assessments will include the ISI, as well as the BDI-II and BAI, STOPBang and International Restless Legs Scale (IRLS), collectively called the Sleep Disorders Screening Battery (SDSB).

All eligible subjects will be provided with an electronic device on which they will complete the sleep diary. Subjects will be trained in the use of this device. Site staff will instruct subjects to complete the diary each morning within 1 hour after morning wake time and will emphasize the importance of doing so. The sleep diary entries will be reviewed by site staff at least weekly throughout the study to ensure subject compliance with completion of the sleep diary and to ensure that study restrictions are met pertaining to duration of time spent in bed. Subjects will also be reminded of study restrictions pertaining to timing of meals and caffeine/alcohol use.

After subjects have completed the sleep diary on at least 7 consecutive mornings, provided that the sleep diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the second Screening Visit (Visit 2a). (Subjects who are not eligible based on sleep diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day –18 and Day –12. On this and all nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. After check-in has been completed, subjects will then undergo an 8-hour PSG recording, to start at the median habitual bedtime (MHB) as calculated from the sleep diary entries. The PSG recording will include channels in the electrode montage to screen for symptoms of sleep apnea and periodic limb movement disorder (PLMD). The PSG will be reviewed for inclusion criteria related to the presence of insomnia and absence of symptoms of sleep apnea and/or PLMD. Subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test. (revised per Amendment 01)

9.1.1.2 Run-In Period

The Run-in Period will begin when eligible subjects are dispensed PBO tablets and will continue until the Baseline Period on Day 1. During the Run-in Period, all subjects will take PBO each night approximately 5 minutes before bedtime (defined as the time the subject intends to try to fall asleep). They will be reminded that they must remain in bed for at least

7 hours each night and maintain a regular bedtime and waketime throughout the study, according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals, and use of caffeine and alcohol.

When subjects have completed the sleep diary on at least 7 consecutive mornings during the Run-in Period, the diary will be reviewed for continued eligibility. Subjects who are still eligible will return to the clinic for the first of 2 consecutive nights on which PSG will be recorded. The first of these 2 nights must be between Day –10 and Day –4. In the evening, before the PSG recording, the safety assessments will be conducted. Study personnel will administer study drug to subjects approximately 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second Screening Visit. Subjects will undergo an 8-hour PSG. The next morning, subjects will complete the sleep diary. The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that it is safe for them to do so. Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects approximately 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will complete the sleep diary. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic after the investigator determines that it is safe for them to do so. Subjects will continue to take study drug at home approximately 5 minutes before bedtime and they will continue to complete the sleep diary each morning within 1 hour after morning wake time. They will again be reminded that they must remain in bed for at least 7 hours each night, maintain a regular bedtime throughout the study, and follow study restrictions with regard to timing of meals and use of caffeine and alcohol. Urine drug test will be performed as described in Section 9.5.2. (revised per Amendment 01)

9.1.1.3 Baseline Period

On Day 1, the Run-in Period will end and the Baseline Period will begin. Subjects will return to the clinic for this visit, and the ISI will be administered. Blood and urine samples will be collected for routine safety assessments, an ECG will be performed, and vital signs and weight will be assessed. In addition, subjects should undergo a urine drug test. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period. (revised per Amendment 01)

9.1.2 Randomization Phase

9.1.2.1 Treatment Period

The Treatment Period will begin on Day 1 and will continue until Day 31. Subjects will be randomized in a double-blind manner, to receive LEM10, or PBO. (revised per Amendment 01)

On the evening of Day1, approximately 5 minutes before the subject's MHB, study drug will be administered and an 8-hour overnight PSG will be initiated. At completion of the PSG

recording the following morning (Day 2), subjects will complete the sleep diary. They may leave the clinic after the investigator determines that is safe for them to do so. On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB, followed by an overnight PSG. On the morning of Day 3, a PK sample will be obtained and subjects will complete the sleep diary. Subjects may then leave the clinic after the investigator determines that it is safe for them to do so. Study drug will be dispensed and subjects will be provided with instructions to continue completing the sleep diary each morning within 1 hour of waketime and taking study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period. On Day 29, subjects will return to the clinic. Study drug will be administered approximately 5 minutes before the subject's MHB, followed immediately by a PSG. Urine drug test will be performed as described in Section 9.5.2. On the morning of Day 30, subjects will complete the sleep diary, and may leave the clinic after the investigator determines that it is safe for them to do so. On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, a PK sample will be obtained. Subjects will complete the sleep diary. Then the ISI, BDI-II and BAI will be administered. Blood and urine samples will be collected for routine safety assessments. An ECG will be performed, and vital signs and weight will be assessed. Then, after the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic. (revised per Amendment 01)

9.1.2.2 Follow-Up Period and End of Study Visit

The Follow-Up Period will begin when the subjects leave the clinic at the end of the Treatment Period. Subjects will cease to take study drug but will continue to complete the sleep diary each morning until the end of study (EOS) Visit.

At least 14 days but no more than 18 days after completion of the Treatment Period subjects will return to the clinic for the EOS Visit. At the EOS Visit, in addition to standard safety assessments, a urine drug test will be conducted, and sleep diaries will be collected. After the End of Study Visit, subjects' participation in the study will be finished.

9.1.2.3 Premature Discontinuation of Study Drug

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug (preferably within 7 days), to complete an Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and 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. All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Randomization

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

9.2.2 Run-In

Insomnia trials are associated with PBO effects. This study will include a PBO Run-in Period to exclude subjects who show a response to PBO.

The Run-in Period will also help to identify and exclude subjects who are not compliant with the sleep diary instructions, duration of time spent in bed, or restrictions on alcohol use. In this regard, it is necessary for the subjects to be taking PBO and to obtain sleep diary data for a minimum of 1 week to adequately evaluate whether there is a PBO response. These sleep diary data recordings will be used to further screen for eligibility, and will serve as baseline values for those subjects who continue to randomization. After this minimum 7 nights of treatment, eligible subjects will have PSG recordings on 2 consecutive nights. These recordings will be used to further screen for eligibility, and will serve as baseline values for those subjects who continue to randomization. (revised per Amendment 01)

9.2.3 Study Duration

In Study 304, the efficacy endpoints, change from baseline for mean LPS, SE, and WASO on Days 29/30, was statistically significantly superior for 10 mg of lemborexant compared to PBO ($P<0.05$). Also, the change from baseline for mean sSOL, sSE, sWASO, and sTST over the first 7 nights and last 7 nights of the Treatment Period were statistically significant for 10 mg of lemborexant compared to PBO ($P<0.05$). Study 304 included 30 days of active treatment. Based on the results of Study 304, it was expected that there would not be a loss of efficacy of lemborexant between 1 week and 4 weeks of treatment. In Study 303, efficacy as determined by sleep diary data showed sustained efficacy through Month 6.

9.3 Selection of Study Population

For overall subjects, approximately a total of 700 subjects will be screened to provide approximately 188 overall randomized subjects. Subjects will be randomized to one of the following treatment arms: LEM10, PBO, in an approximate 1:1 ratio. (revised per Amendment 01)

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. A table providing guidelines on the order in which criteria should be assessed and at what visits can be found in Appendix 2.

9.3.1 Inclusion Criteria

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

1. Chinese male or female, age 18 years or older, at the time of informed consent (in Taiwan only subjects with age 20 years or older are eligible) (revised per Amendment 03)
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥ 3 times per week
   - Duration of complaint ≥ 3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of sSOL ≥30 minutes on at least 3 nights per week in the previous 4 weeks AND/OR sWASO ≥60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At second Screening Visit (Visit 2a) and Run-in Visit (Visit 3a): Sleep diary confirms regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 on at least 5 of the final 7 nights and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00 on at least 5 of the final 7 nights (revised per Amendment 01)
6. At Screening and Baseline: ISI score ≥15 (revised per Amendment 01)
7. Confirmation of current insomnia symptoms, as determined from responses on the sleep diary on the 7 most recent mornings before the first PSG during Screening Period (Visit 2a) and Run-in visit (Visit 3a), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 01)
8. At the second Screening Visit (Visit 2a) and the Run-in visit (Visit 3a): Confirmation of sufficient duration of time spent in bed, as determined from responses on the sleep diary on the 7 most recent mornings before the Visit, such that there are no more than 2 nights with time spent in bed duration <7 hours or >10 hours (revised per Amendment 01)
9. During the Run-in Period, objective (PSG) evidence of insomnia as follows:
   a. LPS average ≥30 minutes on the 2 consecutive baseline PSGs, with neither night <20 minutes and/or
   b. WASO average ≥60 minutes on the two consecutive baseline PSGs, with neither night <45 minutes

   (revised per Amendment 01)
10. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night

11. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

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

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
2. Females of childbearing potential who:

    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
    - total abstinence (if it is their preferred and usual lifestyle)
    - an intrauterine device or intrauterine hormone-releasing system (IUS)
    - a contraceptive implant
    - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
    - have a vasectomized partner with confirmed azoospermia.
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

    It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

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

3. Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
4. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG. A history of risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome) or the use of concomitant medications that prolonged the QTcF interval.

5. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening
6. Any suicidal behavior in the past 10 years
7. Evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal; moderate and severe hepatic impairment; renal including severe renal impairment; neurological including myasthenia gravis; psychiatric disease; or malignancy within the past 5 years other than adequately treated basal cell carcinoma) or chronic pain that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. (revised per Amendment 02) Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded
8. Hypersensitivity to lemborexant or to their excipients
9. Scheduled for surgery during the study
10. Known to be human immunodeficiency virus (HIV) positive
11. Active viral hepatitis (B or C) as demonstrated by positive serology
12. History of drug or alcohol dependency or abuse within approximately the last 2 years
13. A current diagnosis of sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
    - STOPBang score ≥5
    - International Restless Legs Scale score ≥16
14. Apnea-Hypopnea Index >15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second Screening Visit (revised per Amendment 01)
15. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy
16. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping)
17. For subjects who underwent diagnostic PSG within 1 year before informed consent:
    - Age 18 to 64 years: Apnea Hypopnea Index ≥10, or Periodic Limb Movements with Arousal Index ≥10
    - Age ≥65 years: Apnea Hypopnea Index >15, or Periodic Limb Movements with Arousal Index >15
18. BDI-II score >19 at Screening

19. BAI score >15 at Screening
20. Habitually naps during the day more than 3 times per week
21. Excessive caffeine use that in the opinion of the investigator contributes to the subject's insomnia, or habitually consumes caffeine containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and ≥5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation. To be exclusionary, those symptoms must cause distress or impairment in social, occupational and other forms of functioning, and not be associated with other substance, mental disorder or medical condition
22. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3 hours before bedtime for the duration of his/her participation in the study
23. Excluding comorbid nocturia that is causing or exacerbating the insomnia
24. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period). (A list of prohibited concomitant medications is presented in Appendix 3 of protocol)
25. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period)
26. Failed treatment with dual orexin receptor antagonist drugs (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator (revised per Amendment 01)
27. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study (China mainland will be considered as 1 time zone) (revised per Amendment 01)
28. A positive drug test at Screening, Run-in, or Baseline, or unwilling to refrain from use of recreational drugs during the study
29. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5×the half-life, whichever is longer preceding informed consent
30. Previously participated in any clinical trial of lemborexant

9.4 Treatments

9.4.1 Treatments Administered

Test drug

LEM10 or lemborexant-matched PBO will be taken orally in tablet form each night for 30 consecutive nights, approximately 5 minutes before the time the subject intends to try to sleep. (revised per Amendment 01)

Run-In Period

All subjects will receive 1 lemborexant-matched PBO in a single-blind manner during the Run-in Period approximately 5 minutes before the time the subject intends to try to sleep.

Treatment Period (in Randomization Phase)

All subjects will receive 1 tablets as described below, according to the treatment arm to which the subject has been randomized: (revised per Amendment 01)

- LEM10: 1 lemborexant 10 mg tablet
- PBO: 1 placebo tablet matched to lemborexant 10 mg

9.4.2 Identity of Investigational Products

The sponsor will provide lemborexant tablets in strengths of 10 mg and lemborexant-matched PBO, identical in appearance. Tablets will be packaged in blister cards in a double-blind manner. (revised per Amendment 03)

Each subject will be dispensed a single card at the beginning of the Run-in Period and on Day 1. The subject will take 1 tablet a day; a single lemborexant or lemborexant-matched PBO tablet. The PBO Run-in card will contain a 17-day supply of lemborexant-matched PBO tablets per day. Each card for the Treatment Period will contain a 35-day supply of tablets of either lemborexant or lemborexant-matched PBO depending on the dose, in double-blind fashion. (revised per Amendment 01)

9.4.2.1 Chemical Name, Structural Formula of E2006/Lemborexant

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

9.4.2.2 Comparator Drug

PBO to match lemborexant as described in Section 9.4.2 will be used as a comparator drug in the study.

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.

The following information has to be provided:

- For clinical study use only
- Name of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage condition expiration date

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

At Treatment Day 1, subjects will be randomized, in a double-blind manner, to receive LEM10 or PBO in a 1:1 ratio. (revised per Amendment 01) Randomization will be stratified by site and age group (<65 years old; ≥65 years old). Randomization to study treatments will be 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.

Randomization will be performed centrally by an interactive voice and web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment (and after successful completion of study procedures the morning of Day 1), the investigator or designee will call the IxRS to register the subject information. At Randomization (morning of Day 1), the IxRS will assign each subject a unique 6-digit randomization number.

9.4.4 Selection of Doses in the Study (revised per Amendment 01)

Study 311 design includes only LEM10 because 1) LEM10 were statistically significantly effective on both sleep onset and maintenance compared to PBO in Studies 303 and 304, and 2) LEM10 had a larger effect size for LPS than that of LEM5 in Studies 304 and Study 201. Data on efficacy and safety of LEM5 will be extrapolated from data in the overseas studies that included population PK analyses and the Chinese PK parameters in E2006-J086-014 (Study 014). Taken together with the efficacy and safety results for LEM10 in the Phase 1, 2, and 3 studies, only 10 mg dose level were selected for the current study. (revised per Amendment 01)

9.4.5 Selection and Timing of Dose for Each Subject

Throughout the Run-in Period and the Treatment Period, study drug will be taken at home or in the clinic approximately 5 minutes before the subject intends to sleep, on a time schedule that is consistent as possible. Subjects should not eat a meal within 3 hours before taking the study drug.

9.4.6 Blinding

During the Run-in Period of the Prerandomization Phase, single blinding will be in effect such that the subject will be blinded to study treatment but study personnel will not be blinded. During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

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

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject within the last 3 months before Screening (ie, Prior Medications) or during the study, starting on the date of informed consent, will be recorded on the Prior and Concomitant Medication electronic case report form (eCRF) or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the

investigator will record the medical condition on the Medical History and Current Medical Conditions eCRF.

9.4.7.1 Drug-Drug Interactions

Co administration with strong and moderate P450 (CYP3A) inhibitors may moderately increase exposure to lemborexant, and CYP3A inducers may markedly decrease lemborexant exposure. Potential drug interactions with lemborexant are described in further detail in the Investigator's Brochure; prohibited concomitant medications are described in Section 9.4.7.2 and listed in Appendix 3.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (presented in Appendix 3 of protocol) should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period). (revised per Amendment 01)

Prohibited medications include moderate and strong CYP3A inhibitors and all CYP3A inducers. (revised per Amendment 01) Prohibited therapies also include: any treatment for insomnia disorder, including any drugs or non-pharmacological treatment such as cognitive behavioral therapy; medications that are used for the purpose of inducing sleep (hypnotics) or inducing wakefulness (stimulants; except caffeine; see below) and medications that have known sedating effects or alerting effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications but in the opinion of the investigator causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in Appendix 3, 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 during the study, 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 moderate and strong CYP3A inhibitors will not be permitted at any time for any duration of use during the study. (revised per Amendment 01)

9.4.7.3 Caffeine and Alcohol Restrictions

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. (revised per Amendment 01)

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcohol containing drinks on any given day while in the study, and will be instructed not to consume any alcohol within 3 hours before bedtime. A drink will be defined as 285 mL of beer, 150 mL of wine, or 25 mL of liquor. Subjects must not consume any alcohol on days when they are scheduled for a PSG recording. (revised per Amendment 01)

9.4.8 Treatment Compliance

Compliance will be assessed for each study drug by examination of blister packs returned to the investigator at the end of the Run-in and Treatment Periods.

All subjects will be reminded of the importance of taking study medication as directed, ie, the correct number of tablets every night approximately 5 minutes before bedtime, and they will be reminded that their bedtime should be the same throughout the study. Subjects will be told that following these instructions about taking study medication is important for the treatment to be effective. Compliance will be monitored closely and determined at specific visits by tablet count. Tablets will be counted separately for tablets that are matched to lemborexant.

When subjects arrive for Baseline, and the treatment compliance check indicates that a subject has missed any doses, the investigator must use clinical judgment to decide if the subject should continue in the study.

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

9.4.9 Drug Supplies and Accountability

The investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Throughout the duration of the study, study medication will be reconciled on a periodic basis by the CRAs. The investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

At completion of the study, all study medication will be reconciled by the CRO monitor and then returned at the direction of CRO to either CRO or a third party contractor to be retained or destroyed according to applicable local regulations. Prior to any action being taken with study medication after the study is completed the investigator will contact CRO for approval of such action.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include date of birth (or age), sex, and race/ethnicity. (revised per Amendment 04)

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 5 years, except for history of any sleep disorder, which should be lifetime, must be noted in the Medical History and Current Medical Conditions eCRF. Lifetime psychiatric history will also be obtained. A full physical examination will be performed, excluding a urogenital examination unless there are special circumstances and at the discretion of the investigator. The physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). The neurological examination must be conducted by a clinician whose clinical experience ensures that an adequate assessment of domains underlying the exclusion criteria can be performed.

Physical examinations (full or brief) will be performed as described in Section 9.5.1.5.5.

9.5.1.2.2 SLEEP DISORDERS HISTORY AND SCREENING BATTERY

A lifetime history of sleep disorders will be obtained only at the first Screening Visit. For insomnia complaints, this history will include clinical, qualitative assessment and/or confirmation that subjects meet diagnostic criteria for insomnia disorder. The history will also include information regarding habitual sleep timing, bedtime routines, and other aspects of sleep hygiene to determine eligibility and to exclude subjects whose insomnia symptoms appear to be due to poor sleep hygiene or to frequent napping, for example.

For the detection of other sleep disorders, the SDSB will be administered (see below). Upon review of the findings, if a subject endorses more than 2 items on the Symptoms of Narcolepsy Screen, the study site will probe for further clinical information to ascertain whether the subject has a likelihood of a narcolepsy diagnosis.

The SDSB will include the following, to be administered by trained site personnel:

- StopBANG: a list of eight questions to be answered Yes or No, which screens subjects for obstructive sleep apnea (Chung et al., 2008)

- IRLS (International Restless Legs Scale): a subjective scale comprising ten questions, which measures severity of symptoms of restless legs syndrome (Abetz et al., 2006)

9.5.1.2.3 VIRAL TESTING

At the Screening Visit, a 6 mL blood sample will be taken for detection of hepatitis B surface antigen and hepatitis C antibodies, the presence of which would be exclusionary.

9.5.1.2.4 PREGNANCY TESTS FOR WOMEN OF CHILD BEARING POTENTIAL

A serum β-hCG test will be performed at Screening for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 consecutive months. Subsequently, urine pregnancy tests will be conducted for these subjects as specified in the Schedule of Procedures/Assessments (Table 3).

9.5.1.3 Efficacy Assessments

9.5.1.3.1 POLYSOMNOGRAPHY (PSG) (REVISED PER AMENDMENT 01)

Each PSG recording will include an electrode montage with electroencephalography (EEG), electromyography (EMG), electrooculography, and ECG channels, for scoring of sleep parameters and sleep architecture via standard sleep scoring criteria. In addition, the first PSG will include channels for assessment of symptoms of sleep apnea and periodic limb movement disorder.

Trained PSG scorers will score PSG records in 30-second epochs according to standard criteria. The PSG at the second Screening Visit will be used only to calculate the Apnea-Hypopnea Index and the Periodic Limb Movements with Arousal Index for evaluation of eligibility criteria; sleep parameters and sleep architecture will not be evaluated from this PSG. The 2 PSGs obtained during the Run-in Period will be used to a) determine eligibility and b) derive baseline PSG parameters for those subjects who are randomized.

All PSG parameters will be obtained separately for each PSG recording and averaged across the pairs of consecutive PSG nights.

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per time in bed (TIB), calculated as total sleep time (TST)/interval from lights off until lights on
- WASO: minutes of wake from the onset of persistent sleep until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5

minutes or longer] scored as wake or N1, initiated with at least one epoch of wake, after onset of persistent sleep, and including any terminal awakening)

Additional sleep architecture parameters will be also calculated from each PSG, including:

- Sleep onset latency: minutes from lights off to the first epoch of any stage of sleep (N1, N2, N3, rapid eye movement [REM])
- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening could not be interrupted by stage N1, but must have been interrupted by stage N2, N3, or REM
- Number of long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least 1 epoch of wake, after onset of persistent sleep, and including any terminal awakening)
- Percentage of stage wake and sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per TST: NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of sleep (N1, N2, or N3) to first epoch of REM

Each of these PSG-derived variables, with the exceptions of SE, REM episode frequency and duration, mean REM/NREM cycle duration, and REM latency, were also calculated by hour and by half of the 8-hour time interval in bed.

9.5.1.3.2 ELECTRONIC SLEEP DIARY

The sleep diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the study. Sleep diary entries may be maintained in paper format as a backup to the electronic sleep diary, if necessary. This sleep diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety. In addition, the sleep diary will include questions that relate to morning sleepiness.

Subjects must comply with requirements for completion of the sleep diary. Failure to comply will require discussion with the Medical Monitor and may result in discontinuation of the subject from the study.

Sleep Parameters

- sSOL: estimated minutes from the time that the subject attempts to sleep until sleep onset
- sWASO: sum of estimated minutes of wake during the night after initial sleep onset until the time that the subject stopped trying to sleep for the night
- sTST: derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
- sSE: proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reported attempting to sleep until the time the subject stopped trying to sleep for the night, and time spent asleep derived from subjective time spent in bed minus sWASO

Sleep architecture parameters will be calculated as described above under assessments. (revised per Amendment 01)

Quality of Sleep and Morning Sleepiness

The sleep diary will be used to assess the subject's global perception of quality of sleep on the previous night with the following question: "How would you rate the quality of your sleep last night?" Subjects will rate the quality of their sleep on a scale from 1 to 9, with 1 being extremely poor and 9 being extremely good.

The sleep diary will be used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" Subjects will rate their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely sleepy and 9 being extremely alert.

9.5.1.3.3 INSOMNIA SEVERITY INDEX

The ISI is a 7-item self-report questionnaire assessing the nature, severity and impact of insomnia (Bastien et al., 2001). The dimensions evaluated are severity of: sleep onset, sleep maintenance, early-morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning, noticeability of the sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (from 0=no problem to 4=very severe problem), yielding a total score from 0 to 28.

9.5.1.3.4 BECK DEPRESSION INVENTORY-II

The BDI-II is a 21-question multiple-choice self-report questionnaire that subjects will use to rate the presence, frequency, and severity of symptoms of depression using a 4-point Likert scale (Arnau et al., 2001). Scores on the BDI-II range from 0 to 63, with higher scores indicating higher levels of depressive symptoms. Subjects with BDI-II scores >19 will be excluded from participation.

9.5.1.3.5 BECK ANXIETY INVENTORY

The BAI is a 21-question multiple-choice self-report inventory that subjects will use to rate the presence, frequency, and severity of symptoms of anxiety using a 4-point Likert scale (Carney et al., 2011). Scores on the BAI range from 0 to 63, with higher scores indicating higher levels of anxiety symptoms. Subjects with scores on the BAI >15 will be excluded from participation.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

A single blood sample (4 mL per blood draw) for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be taken at predefined visits. The time and date of the 2 most recent lemborexant doses administered before each sample will be documented. The handling and shipment of blood samples will be described in a manual to be provided to the study sites. Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) will be measured using validated liquid chromatography-tandem mass spectrometry assay methods.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study including after the last dose of study drug, and at the End of Study, ET, and Unscheduled Visits. (revised per Amendment 01)

9.5.1.5.1 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 drugs is lemborexant.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note:

Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)

An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. 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. Serious AEs (SAEs) 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 eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms (>450 ms) and there is an increase of more than 60 ms (>60 ms) from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

AEs in clinical investigation subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes. All AEs encountered during the clinical study will be reported on the eCRF.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

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

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF 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

9.5.1.5.3 LABORATORY MEASUREMENTS

Blood and urine samples will be collected for the clinical laboratory tests as listed in Table 1. Clinical laboratory tests are to be performed according to the schedule in Table 2. Subjects should be in a seated or supine position during blood collection.

Viral testing for hepatitis B and C will be conducted from a blood sample obtained at Screening. The specific test for hepatitis B is the surface antigen panel (HBsAg) with confirmation as needed. The specific tests for hepatitis C are the hepatitis C virus (HCV) antibody immunoglobulin G (IgG), with confirmation as needed using the HCV score.

A 30 mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 3). These samples will be tested for common drugs of abuse: eg, cocaine, cannabinoids, phencyclidine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, globulin, glucose, iron, 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.

Serum pregnancy tests and urine drug tests will be collected for screening purposes. A dipstick will be used for urine pregnancy testing and urine drug testing, to be performed at time points shown in the Schedule of Procedures/Assessments (Table 3). The total blood volume to be drawn for laboratory measures in the study (Table 2) will be indicated on the ICF.

Table 2 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments (revised per Amendment 03)

	Volume per Sample Collection (mL)	Collection Time points	Total Volume Collected (mL)
Clinical laboratory tests[a]	7	Screening Day 1 Day 31 End of Study	28
Pregnancy testing[b]	N/A	Screening	N/A
Viral tests	8.5	Screening	8.5
Pharmacokinetic sampling[a]	4	Day 2, Day 3 Day 30, Day 31	16

Table 2 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments (revised per Amendment 03)

Total	52.5 mL

a: Clinical laboratory tests and/or pharmacokinetic sampling will also be conducted at ET visits, and may also be obtained at unscheduled visits at the discretion of the investigator.
b: Included in the clinical laboratory test volume

Clinical laboratory tests during the study will be performed by a 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. Laboratory certification as available will be included in the final clinical study report for this study. Only when there is an unavoidable reason that the central laboratory cannot be used (eg, lockdown by coronavirus disease pandemic), the clinical laboratory tests can be performed by the local laboratory instead of the central laboratory. For consistency for a given subject, if the local laboratory had been used at baseline, it should be used continuously even if the central laboratory can be used later on. (revised per Amendment 05)

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

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], and body temperature [in centigrade] will be obtained at the visits designated on the Schedule of Procedures/Assessments (Table 3) by a validated method. Blood pressure and pulse will be measured after the subject has been in a sitting position for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. Validated methods will be used for all vital sign measurements, and values will be recorded. Height (cm), and weight (kg) will also be measured.

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.

9.5.1.5.5 Physical Examinations

Physical examinations (full or brief) will be performed as designated on the Schedule of Procedures/Assessments (Table 3). At Screening and at the EOS/ET visit, a full physical examination will be conducted, including evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin. The full physical examination will include a brief neurological examination to assess possible impairment in major

functions (ie, motor, cerebellar, sensory, major pathological reflexes). A urogenital examination will only be required in the presence of clinical symptoms related to this region and at the discretion of the investigator. At other study visits as designated in Table 3, a brief physical examination will be conducted to assess health status by brief evaluation of the head, eyes, ears, nose, throat, heart, lungs, abdomen, and extremities, and other physical conditions of note. Documentation of the physical examinations, including the brief neurological examinations, will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE eCRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

ECGs will be obtained as designated on the Schedule of Procedures/Assessments (Table 3).

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

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

Not applicable.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for this study.

Table 3 Schedule of Procedures / Assessments in Study E2006-J086-311 (revised per Amendment 01 and 02)

Phase	**Prerandomization**								**Randomization**										
Period	**Screening**			**Run-in**				**BL**	**Treatment[a]**								**Follow-Up**	**ET[b]**	**UNS**
Visit	**1**	**2a**	**2b**	**3a**	**3b**	**4a[c]**	**4b**	**5a**	**5b**	**5c**	**6a[d]**	**6b**	**7a**	**7b**	**8a[e]**	**8b**	**EOS[f]**		
Target Study Day	**–35 to –19**	**–18 to –12**	**–17 to –11**	**–10 to –4**	**–9 to –3**	**–9 to –3**	**–8 to –2**	**1**	**1**	**2**	**2**	**3**	**29 –2/+5**	**30 –2/+5**	**30 –2/+5**	**31 –2/+5**	**44**		
Procedures/ Assessments																			
Informed consent	X																		
Demographics	X																		
Inclusion/exclusion criteria[g]	---------->																		
Height	X																		
Weight	X							X								X	X	X	
Clinical laboratory tests[h]	X							X								X	X	X	X
Serology (Hepatitis B and C)[i]	X																		
Serum pregnancy test (β-hCG)[j]	X																		
Urine pregnancy test[j]		X		X				X					X				X	X	X
Vital signs	X							X								X	X	X	X
12-lead ECG[k]	X							X								X	X	X	X
Sleep, medical, and psychiatric history	X																		
ISI	X							X								X			
SDSB[l]	X																		
Physical exam[m]	X							X								X	X	X	X

Table 3 Schedule of Procedures / Assessments in Study E2006-J086-311 (revised per Amendment 01 and 02)

Phase	**Prerandomization**								**Randomization**										
Period	**Screening**			**Run-in**				**BL**	**Treatment[a]**								**Follow-Up**	**ET[b]**	**UNS**
Visit	**1**	**2a**	**2b**	**3a**	**3b**	**4a[c]**	**4b**	**5a**	**5b**	**5c**	**6a[d]**	**6b**	**7a**	**7b**	**8a[e]**	**8b**	**EOS[f]**		
Target Study Day	**–35 to –19**	**–18 to –12**	**–17 to –11**	**–10 to –4**	**–9 to –3**	**–9 to –3**	**–8 to –2**	**1**	**1**	**2**	**2**	**3**	**29 –2/+5**	**30 –2/+5**	**30 –2/+5**	**31 –2/+5**	**44**		
Procedures/ Assessments																			
Prior / concomitant medications	----------																		→
Beck Depression Inventory II	X															X			
Beck Anxiety Inventory	X															X			
Urine drug test	X	X		X		X		X			X		X		X		X	X	X
Sleep diary[n]	----------																		→
PK blood sampling[o]											X	X			X	X			X
Polysomnography[p]		X		X		X			X		X		X		X				
Randomization									X										
Dispense study drug[q]			X						X										
Study drug at bedtime[r]		----------														→			
Retrieve unused study drug								X					X						
Check study drug compliance[s]				X				X					X						
Admission to clinic		X		X				X					X						
Discharge from clinic			X				X					X				X			
Discharge from study																	X	X	
Adverse events[t]	----------																		→

BL = baseline, ECG = electrocardiogram, EMG = electromyography, EOS = end of study; ET = early termination, ISI = Insomnia Severity Index, PK = pharmacokinetic, PSG = polysomnography, SDSB = Sleep Disorders Screening Battery, UN = unscheduled visit.

a: AE, concomitant therapy will be confirmed by telephone on Day 14 (±2). Diary entries will be reviewed by site staff at least weekly throughout the study to ensure subject compliance with completion of the sleep diary, drug compliance and to ensure that study restrictions are met pertaining to duration of time spent in bed. Subjects will also be reminded of study restrictions pertaining to timing of meals and caffeine/alcohol use.
b: Subjects who discontinue the study early for any reason after Randomization at Visit 5 should complete this visit.
c: Must be consecutive with Visit 3a.
d: Must be consecutive with Visit 5b.
e: Must be consecutive with Visit 7a.
f: Must occur 14 – 18 days after Visit 8.
g: Inclusion and exclusion criteria to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2.
h: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
i: Viral screening for hepatitis B (HBsAg) and hepatitis C (HCV antibody IgG) will be conducted.
j: Female subjects of child-bearing potential only.
k: The ECG should be repeated if an abnormality is observed. If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as >450 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.
l: The Sleep Disorders Screening Battery includes: STOPBang, International Restless Legs Scale.
m: Full physical examination (including a brief neurological exam) will be carried out at Screening and EOS and ET (if applicable). Brief physical examinations will be carried out at other visits.
n: Should be completed, within 1 hour of morning waketime, on every day of the study from Screening until the end of the study, and reviewed for eligibility before initiating any study assessments at Visit 2 and Visit 3.
o: One PK blood sample (approximately 4 mL) will be obtained at the following timepoints: within 2 hours predose Day 2 and Day 30; within 1 hour after morning waketime on Day 3 and Day 31.
p: PSG recordings will include a standard montage on all PSG nights. Diagnostic channels (respiratory effort, airflow, leg EMG) will be added to the standard montage on the PSG at Visit 2. All PSG visits will require an overnight stay in the clinic. At least 2 nights must intervene between the second BL PSG (Visit 4b) and BL (Visit 5a).
q: On Visit 5b, 6a, 7a, 8a, study drug will be administered to the subject by clinical staff. The study drug will be dispensed to subjects on Visit 6b, on days that the subjects are not admitted to the clinic subjects will self-administer study drug.
r: First dose of study drug is taken by the subject on the first night at home after Visit 2b. On the days that subjects are admitted to the clinic, study drug will be administered to the subject by clinical staff. The first dose of active study drug will be administered at Visit 5b. The last dose of active study drug will be administered at Visit 8a. On days that the subjects are not admitted to the clinic subjects will self-administer study drug. All study drug administration must be approximately 5 minutes of bedtime (defined as the time the subject attempts to sleep).
s: Subjects will be questioned about study drug compliance upon check-in at Visits 3a, 5a, and 7a. Tablet counts for study drug compliance will be done after end of Run-in Period and end of Treatment Period.
t: At each visit, subjects will be asked whether they have had a fall since the previous visit.

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments is shown in Table 3.

9.5.3 Appropriateness of Measurements

Completion of sleep diaries by subjects is considered to be an appropriate method to measure changes in subjective sleep parameters, thereby allowing assessments of secondary efficacy in this study. The advantages of the electronic sleep diary to be used in this study include that the questions and instructional text have been adapted from sleep diaries that were developed by clinicians and researchers with expertise in insomnia disorder, and have undergone linguistic validation and cognitive debriefing to optimize their use in this study. The sleep diary will include questions to assess the subject's rating of sleep quality each night and sleepiness/alertness level in the morning.

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of both nighttime sleep and daytime impairment complaints, the ISI will be evaluated for changes from baseline. These measures have been used in studies evaluating the impact of treatment for insomnia on patients' global perceptions of sleep quality and quality of life. Together these measures will provide a broad evaluation of the effects of lemborexant on each patient's sleep, daytime functioning, quality of life and productivity.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. Additional safety related assessments include evaluation of morning sleepiness and rebound insomnia, which will be measured using the validated sleep diary.

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

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported to regulatory authorities and the Sponsor or designated CRO on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

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

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

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

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

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

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

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

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

9.5.4.3 Reporting of Events Association with Special Situations

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

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

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (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 eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Not applicable.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

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

code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

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

9.5.5 Completion/Discontinuation of Subjects

For purposes of entering subject disposition in the eCRF, a subject will be considered to have completed the study per protocol after the End of Study visit has been completed. The subject may elect to discontinue the study at any time for any reason. Subjects who discontinue study drug prematurely at any time after randomization at Visit 5 (Study Baseline) will be encouraged to return to the site as soon as practicable (preferably within 7 days). (revised per Amendment 02) These subjects will be encouraged to continue to complete all study assessments (excepting PK samples, which will not be taken), including the sleep diary, and to return for all subsequent clinic visits, without the administration of study medication.

Subjects will undergo an ET Visit and an EOS Visit, as described in the Schedule of Procedures/Assessments (Table 3).

Subjects who withdraw because of an AE should also undergo a urine drug test.

If the investigator or sponsor discontinues a subject from the study prematurely, the investigator will promptly explain to the subject involved that the study will be discontinued for that subject and will provide appropriate referral for 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. This information will be recorded in the eCRF.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow up, subject choice, lack of therapeutic effect, or administrative/other. Discontinuations due to noncompliance with alcohol restrictions will be assigned to “administrative/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 eCRF.

A subject removed from the study for any reason will not be replaced. In some circumstances, a subject who screen fails before the Run-in period may be rescreened following consultation with the Sponsor. Any such subject will be assigned a new subject identification number.

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 eCRF.

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

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

9.6.1 Data Collection

Data required by the protocol will be collected in a validated data management system that is compliant with all regulatory requirements. These data include eCRFs, computer tablets and electronic sleep diaries. As defined by C-GCP, the eCRF 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 eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs 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 eCRF 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 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 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.

All statistical tests will be based on the 5% level of significance (2 sided).

9.7.1.1 Study Endpoints (revised per Amendment 04)

The following endpoints will be analyzed for LEM10 compared to PBO.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint will be change from baseline of objective LPS during the last 2 nights of treatment of LEM10 compared to PBO.

9.7.1.1.2 SECONDARY ENDPOINTS

- Change from baseline of objective SE during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of objective WASO during the last 2 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSOL during the last 7 nights of 1 month of treatment of LEM10 compared to PBO
- Change from baseline of sSE during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of sWASO during the last 7 nights of treatment of LEM10 compared to PBO
- Change from baseline of PSG parameters (LPS, SE, WASO) over the first 2 nights of 30 nights of LEM10 compared to PBO
- Safety and tolerability of lemborexant
- Change from Study Baseline in insomnia severity and daytime functioning, assessed as the ISI total number and total score from the 4 items related to daily function on the ISI after 1 month of treatment with LEM10 compared to PBO

- Rebound insomnia endpoints as assessed from the sleep diary during the Follow-Up Period
- Morning residual sleepiness during treatment and following completion of treatment

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Subjective quality of sleep
- Sleep architecture
- Effects on BDI–II and BAI
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose efficacy measurement.
- The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding will be specified in the SAP.
- The PK Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least one quantifiable plasma concentration of lemborexant or its metabolites, with adequately documented dosing history.

9.7.1.3 Subject Disposition

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

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic variables include age, height, weight, and body mass index (BMI); categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (less than 18.5, 18.5 to less than 25, 25 to 30, above 30), race and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using LPS, SE, WASO, sSOL, sSE, sWASO, sTST, and ISI. The BDI-II and BAI scores will also be summarized at Study Baseline.

The demographic data will be summarized by subgroups of age group, sex, BMI group and race. The above tables will be produced for the FAS if it differs from the Safety Analysis Set.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11 digit code using the World Health Organization Drug Dictionary (WHO DDE/HD Mar 2018 or latest version). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term (PT). If the Safety Analysis Set and FAS differ substantially, then the prior and concomitant medication summaries will be repeated on the FAS.

Prior medications are defined as medications that stopped before the first dose of study drug, where study drug includes PBO during the Run-in Period.

Concomitant medications are defined as medications that (1) started before the 1st dose of study drug (including the Run-in Period) and are continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug (including the Run-in Period) to the last dose day plus 14 days. All medications will be presented in subject data listing.

Summaries of concomitant medications will also be separately subgrouped into Safety Analysis Set. (revised per Amendment 01)

9.7.1.6 Efficacy Analyses

The efficacy analyses will be performed on the FAS except the per protocol analysis will be performed on the PP. (revised per Amendment 01)

Definitions of Baseline

Baseline data are captured during the Run-in and Baseline Period.

9.7.1.6.1 ANALYSIS FOR THE PRIMARY ENDPOINT (REVISED PER AMENDMENT 01)

Null Hypothesis: For objective LPS, no difference exists in the mean change from Study Baseline to the last 2 nights of Month 1 of treatment with LEM10 compared with PBO.

Alternative Hypothesis: For objective LPS, a difference exists in the mean change from Study Baseline the last 2 nights of Month 1 for LEM10 compared with PBO.

The objective LPS change from Baseline (the mean of Days 1 and 2, and the mean of Day 29 and 30) will be analyzed using the mixed effect model repeated measurement analysis (MMRM) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), site, age group (<65 years old; ≥65 years old), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. Factor "Site" will be defined in the SAP before database lock. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputations (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV-subjects who completed primary efficacy assessments without missing values). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The *P*-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided.

Subgroup analyses and additional sensitivity analysis will be performed as appropriate.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described above will be repeated on subjects who completed all efficacy assessments and have no missing values.
- As-treated analysis: The same primary efficacy analyses (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.
- MMRM analysis assuming missing at random (MAR): The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are MAR.
- MI Imputation assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows)

Study days where results are available	1	2	29	30
Pattern 1	x	x	x	x
Pattern 2	x	x	x	–
Pattern 3	x	x	–	–
Pattern 4	x	–	–	–

x: result present; – : result missing

9.7.1.6.2 SECONDARY EFFICACY ANALYSIS (REVISED PER AMENDMENT 04)

The other efficacy endpoints (change from Baseline of the following for LEM10 compared to PBO; mean objective SE, mean objective WASO, mean sSOL, mean sSE, and mean sWASO at the first 7 nights and last 7 nights of treatment; ISI total number and total score of 4 items of daytime functioning after 1 month of treatment) will be analyzed using the MMRM, assuming the missing values are missing at random (MAR). The sSOL will be implemented on the log-transformation. Subgroup analyses will be defined SAP in detail.

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep diary data from the Follow-Up Period will be compared to sleep diary data from the Screening Period to assess whether subjects experience rebound insomnia. To assess rebound insomnia, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the first 3 nights and each of the 2 weeks of the Follow-Up Period the proportion of subjects whose corresponding value for sSOL or sWASO exceeds the corresponding Screening Period value by 5 minutes will be summarized by treatment group and compared to PBO. The percentage of 'rebounders' between LEM10 and PBO group will be analyzed using a chi-square test. To assess statistical significance using the continuous data, the data will be analyzed using ANCOVA. The LS mean of each of the first 3 nights and each week of the Follow-Up Period will be compared to the Screening Period between LEM10 and PBO. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-Up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen will be considered to evaluate whether clinically meaningful rebound insomnia is present.

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the sleep diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-Up Period will be analyzed using MMRM assuming MAR.

9.7.1.6.3 EXPLORATORY EFFICACY AND PHARMACODYNAMIC ANALYSES

The change from Baseline for the mean score of the quality of sleep item on the sleep diary will be analyzed, to consider the subjective quality of sleep, using MMRM, assuming MAR for the mean of the first 7 days after 1 month of treatment. The change from Baseline (at Screening) for BDI-II and BAI will be analyzed using ANCOVA including treatment and Baseline. Other efficacy measures will be tabulated, and may be plotted, but will not be statistically analyzed.

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 its metabolites M4, M9, and M10 plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and its metabolites M4, M9, and M10 plasma concentrations by dose and blood sampling point.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

There are no variables in this study that are primarily designated as PD variables. These analyses are described in the Secondary Efficacy and Pharmacodynamic Analysis Section 9.7.1.6.2 and Exploratory and Pharmacodynamic Analyses Section 9.7.1.6.3.

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Not applicable.

9.7.1.7.4 PHARMACOGENOMIC ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set.

The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs and weight, along with change from baseline in laboratory safety test variables, ECGs, and vital sign and weight measurements, will be summarized by treatment group using descriptive statistics.

Secondary and exploratory endpoints may be additionally presented graphically or analyzed by modeling methods if warranted.

Details of all of analysis will be specified in the SAP.

9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized descriptively. The exposure data with LEM10 will be summarized for: the number (percent) of subjects who completed ≥7 days or ≥ 30 days.

Compliance will be calculated on the basis of number of tablets dispensed, lost and returned. Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and >120%.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) 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 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment (including the Run-in Period), having been absent at pretreatment (before the Run-in Period) or

- Reemerges during treatment, having been present at pretreatment (before the Run-in Period) 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. AEs will be classified as TEAEs up to 14 days after the last study treatment. (revised per Amendment 04)

The TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number of events as TEAEs by SOC and PT will also be summarized.

The number of subjects (percentage)/events with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number of subjects (percentage)/events with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]). Treatment related TEAEs include those events considered by the investigator to be related to study treatment.

The number of subjects (percentage)/events 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 of subjects (percentage)/events 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.

The number of subjects (percentage)/events with preferred term related to drug abuse liability will be summarized.

9.7.1.8.3 LABORATORY VALUES

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this study. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum for continuous variables, and number and percentage for categorical variables) for the laboratory parameters and changes from Study Baseline will be evaluated by treatment group and visit.

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 will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the Study Baseline LNH classification to the LNH classification by treatment group.

Clinical laboratory results post Study Baseline will be evaluated for markedly abnormal values. A laboratory test will be considered markedly abnormal if the result worsens to meet Eisai grading criteria for laboratory values limit of Grade 2 or higher. If the Grade 2 limit is missing, the Grade 1 limit will be considered. Appendix 1 presents the Eisai grading criteria for laboratory values that were used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

9.7.1.8.4 VITAL SIGNS AND WEIGHT

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from Study Baseline will be presented by visit and treatment group.

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range. Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges (Table 4) will also be presented for change from Study Baseline (Safety Analysis Set) by treatment group and by time point.

Table 4 Clinically Notable Vital Sign Ranges

Variable	Criterion Value[a]	Change Relative to Study Baseline[a]	Clinically Notable Range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

BP = blood pressure, H = high, L = low

a. Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to Study Baseline.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from Study Baseline (Safety Analysis Set) will be presented by treatment group. Shift tables will present changes from Study Baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by time point.

For each subject, the maximum observed QTcF, the corrected QT interval calculated using Bazett's formula (QTcB), and the maximum prolongation from Study Baseline in QTcF will be compiled. Categorical analyses of subjects (number and percent) with maximum observed QTcF values >450 ms, >480 ms, and >500 ms and maximum prolongations (from Study Baseline) in QTcF >30 ms and >60 ms will be presented by treatment group and by time point. Categorical analyses of subjects (number and percent) with maximum observed PR values >220 ms, and QRS values >120 ms will be presented by treatment group and by time point.

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable.

9.7.1.9 Other Analyses

Secondary and exploratory endpoints may be additionally presented graphically or analyzed by modeling methods if warranted. Details of all of analyses will be specified in the SAP.

9.7.2 Determination of Sample Size (revised per Amendment 01)

The sample size was considered based on LPS for each comparison between Study 201 and Study 304. For LEM10 on Days 29 and 30, we assume the effect size that mean difference divided by common standard deviation as –0.411 under logarithm transformation. Therefore, to detect a difference in LPS comparing LEM10 with PBO, at least 94 subjects per group

(total 188) will be needed for a 0.05 α-level, 2-sided test and more than 80% power based on above assumption.

9.7.3 Interim Analysis (revised per Amendment 01)

This is a fixed design. There is no interim analysis for efficacy and no alpha spending before final analysis. However a blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, may be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment.

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

Abetz L, Arbuckle R, Allen RP, Garcia-Borreguero D, Hening W, Walters AS, et al. The reliability, validity and responsiveness of the International Restless Legs Syndrome Study Group rating scale and subscales in a clinical-trial setting. Sleep Med. 2006;7:340–9.

Arnau RC, Meagher MW, Norris MP, Bramson R. Psychometric evaluation of the Beck Depression Inventory-II with primary care medical patients. Health Psychology 2001;20(2):112-9.

Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297-307.

Carney CE, Moss TG, Harris AL, Jack D, Edinger JD, Krystal AD. Should We Be Anxious When Assessing Anxiety Using the Beck Anxiety Inventory in Clinical Insomnia Patients? J Psychiatr Res 2011;45(9):1243–9.

Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. STOP Questionnaire A Tool to Screen Patients for Obstructive Sleep Apnea. Anesthesiology 2008;108:812–21.

Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;15:S7-10.

Soldatos CR, Allaert FS, Ohta T, Dikeos DG. How do indivisuals sleep around the world? Results from a single-day survey in tem countries. Sleep Medicine. 2005;6:5-13.

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/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

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

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol.

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 and remote monitoring will be conducted between onsite monitoring visits 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 eCRFs 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 to IRB/IEC review.

Source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, ECGs, EEGs) regardless of how these images are stored, including microfiche and photographic negatives
- Quality of life or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as source document. Any correction to entries made on the eCRF 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 eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents. The investigator agrees to allow direct access to source documents and study facilities to sponsor representative(s), monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative.

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 eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study. (revised per Amendment 01)

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

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

11.11 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/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

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

11.12 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

	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

	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

	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 Inclusion/Exclusion Criteria Schedule

Inclusion/exclusion criteria (Section 9.3.1 and Section 9.3.2) will be obtained at study visits as shown below. (revised per Amendment 01)

Visit Name	V1, V2a	V3a	V5a
	Screening	Run-in	Treatment Baseline
Inclusion Criterion Number	1, 2, 3, 4, 5, 6, 7, 8, 10, 11	5, 7, 8, 9	6
Exclusion Criterion Number	1 – 30	1, 20, 21, 22, 23, 24, 25, 27, 28	1, 9, 20, 21, 22, 27, 28

Appendix 3 List of Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	–
Anticonvulsants with known sedating effects	Barbiturates Benzodiazepines GABA analogues Hydantoins Phenyltriazines
Antihistamines (centrally-acting H1, including over the counter)	Diphenhydramine HCl Carbinoxamine Doxylamine Dimenhyrinate Triprolidine Bromopheniramine Chlorphemamine Hydroxazine
Antihistamines with known sedating effects	Non-sedating, eg, Claritin ™ is not prohibited
Anxiolytics with known sedating effects	Lorazepam Alprazolam Buspirone
Moderate CYP3A inhibitors	aprepitant cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil

Strong CYP3A inhibitors	Amiodarone Bocepravir Clarithomycin Cobicistat Conivaptan Danoprevir Fluvoxamine Idelalisib Indinavir Itraconazole Ketoconazole Lopinavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telapravir Telethromycin Tipranavir Troleandomycin Voriconazole
CYP3A inducers	Carbamazepine St. John's Wort Phenobarbital Troglitazone Phenytoin Rifabutin Rifampin Bosentan Efavirenz Etravirine Lersivirine Modafinil Nafcillin Talviraline Thioridazine

Hypnotics	Melatonin Prescribed or OTC
Herbal preparations with sedating effects	Semen Ziziphi Spinosae Caulis Polygoni Multiflori Tuckahoe Fructus Gardeniae Polygala tenuifolia Angelica sinensis Bupleuri Radix Licorice Rehmannia glutinosa Salvia miltiorrhiza Ligusticum chuanxiong Or any other herbal medication that fit into this class by investigator's judgement
MAOIs	_
Opioid Analgesics	_
Muscle relaxants (centrally-acting) with known sedating effects	GABA analogues Hydantoins Phenyltriazines
Stimulants	Amphetamines Modafinil Armodafinil Methylfenidate
Other	Warfarin, heparin, ticlopidine Non-stimulant diet pills Systemic isoretinoin Systemic glucocorticoids Tryptophan

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-J086-311

Study Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder

Investigational Product Name: E2006/lemborexant

SIGNATURES

Authors: (revised per Amendment 05)

PPD PPD PPD PPD PPD

Neurology Business Group, Eisai China Inc.

Date

PPD PPD PPD PPD PPD

Neurology Business Group, Eisai Inc.

Date

PPD PPD PPD PPD PPD

Medicine Development Center, Eisai Co., Ltd.

Date

PPD PPD PPD PPD

Medicine Development Center, Eisai Co., Ltd.

Date

SPONSOR SIGNATURE PAGE

Study Protocol Number:	E2006-J086-311
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant

Head, Medicine Development Center, Eisai Co., Ltd.	Signature	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-J086-311
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study of the Efficacy and Safety of Lemborexant in Chinese Subjects with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with China Good Clinical Practice (C-GCP), including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date