REVISION HISTORY

Previous Version: V3.0 (per Amendment 02) Current Version: V4.0 (per Amendment 03) Date of Revisions: 14 Sep 2023		
Change	**Rationale**	**Affected Protocol Sections**
Changed the laboratory for bacteria in urine tests from the central laboratory to local laboratories.	To monitor the subject's safety properly.	Section 9.5.1.4.3

Previous Version: V2.0 (per Amendment 01) Current Version: V3.0 (per Amendment 02) Date of Revisions: 28 Sep 2022		
Change	**Rationale**	**Affected Protocol Sections**
Analysis Sets Per Protocol (PP), added a brief description clarifying that the evaluability criteria will be determined before database lock and will be specified in the SAP.	To meet the regulatory advice from MFDS	Section 2 – Analysis Sets Section 9.7.1.2
Specified that a centralized randomization technique will be used as the allocation method.	To clarify the allocation method.	Section 9.4.3
Corrected language about a timing of blood sampling	Correction	Section 9.5.1.3.1 Section 9.5.1.4.3
Corrected volume per sample collection for blood samplings	Correction	Section 9.5.1.4.3 Section 9.5.2.1
Revised the title of Sponsor.	For Sponsor's organizational changes	SPONSOR SIGNATURE PAGE
Removed language from some definitions of grading for laboratory values	To define the gradings by values only	Section 12, Appendix 1

Previous Version: V1.0 (original protocol) Current Version: V2.0 (per Amendment 01) Date of Revisions: 12 May 2021		
Change	**Rationale**	**Affected Protocol Sections**
No. of sites, increased from 7 sites to 9 sites	To meet the study timeline	Section 2 – Sites Section 6
Dosage of lemborexant to be examined in the primary efficacy parameter, changed from lemborexant 10 mg to lemborexant 5 mg. Accordingly, dosage of lemborexant to be examined in the secondary efficacy parameter (LPS), changed from lemborexant 5 mg to lemborexant 10 mg. In addition, the order of listing for the dosages of lemborexant in objectives, changed from "10 mg to 5 mg" to "5 mg to 10 mg".	To meet the regulatory advice from the MFDS	Section 2 – Objectives Section 2 – Statistical Methods Section 2 – Sample Size Rationale Section 8 Section 9.7.1.1 Section 9.7.2
Study design, randomization ratio to LEM5, LEM10, and PBO, changed from 1:1:1 to 2:2:1.	As a result of revision of the sample size rationale to meet the regulatory advice from the MFDS	Section 2 – Study Design Section 2 –Number of Subjects Section 2 – Sample Size Rationale Section 9.1 Section 9.3 Section 9.7.2
Number of subjects, changed from 45 to 60. Number of subjects randomized to PBO, LEM5 and LEM10, changed from 15, 15 and 15 to 12, 24 and 24, respectively.	To meet the regulatory advice from MFDS	Section 2 – Study Design Section 2 –Number of Subjects Section 2 – Sample Size Rationale Section 9.1 Section 9.3 Section 9.7.2
Corrected exclusion criterion no. 13, changed STOPBang score from ≥15 to ≥5	To correct a typo pointed out by the MFDS	Section 2 – Exclusion Criteria Section 9.3.2
Efficacy Assessments, added sleep architecture parameters	To meet the regulatory advice from MFDS	Section 2 – Efficacy Assessments Section 9.5.1.2.1
CCI [redacted]	To meet the regulatory advice from MFDS	Section 2 – Exploratory Endpoint Section 9.7.1.1.3
Analysis Sets, corrected the definition of FAS from "had at least 1 postdose SE data of	To correct a typo. To clarify that the postdose PSG data required for FAS will be obtained only on Day 30.	Section 2 – Analysis Sets Section 9.7.1.2

Previous Version: V1.0 (original protocol) Current Version: V2.0 (per Amendment 01) Date of Revisions: 12 May 2021		
Change	**Rationale**	**Affected Protocol Sections**
PSG" to "had LPS data from the PSG on Day 30"		
Analysis Sets of PP, added a brief description that details of the evaluability criteria will be determined before database lock and will be specified in the SAP.	To meet the regulatory advice from MFDS	Section 2 – Analysis Sets Section 9.7.1.2
Efficacy Analyses, added a brief description that the main analysis group for the primary endpoint is FAS	To meet the regulatory advice from MFDS	Section 2 – Efficacy Analyses Section 9.7.1.6
CCI [redacted]		
Revised sample size rationale	To meet the regulatory advice from MFDS	Section 2 – Sample Size Rationale Section 9.2.4 Section 9.7.2
Updated worldwide marketing authorization status	Update	Section 7.1
Updated prohibited concomitant medications	Update	Section 12, Appendix 3

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-J082-204
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Pharmacodynamics of Lemborexant in Korean Subjects with Insomnia Disorder
Sponsor	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan
Sponsor's Investigational Product Name:	E2006/lemborexant
Indication:	Insomnia
Phase:	2
Approval Date:	V1.0 14 Sep 2020 (original protocol) V2.0 12 May 2021 (per Amendment 01) V3.0 28 Sep 2022 (per Amendment 02) V4.0 14 Sep 2023 (per Amendment 03)
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Pharmacodynamics of Lemborexant in Korean Subjects with Insomnia Disorder

Investigators

To be determined

Sites

Approximately 9 Sites in South Korea (revised per Amendment 01)

Study Period and Phase of Development

First subject in to last subject out: Approximately 12 months

Phase 2

Objectives

Primary Objective

- To evaluate, using polysomnography (PSG), the treatment difference between lemborexant 5 mg (LEM5) and placebo (PBO) on latency to persistent sleep (LPS) on Day 30 (revised per Amendment 01)

Secondary Objectives

- To evaluate, using PSG, the treatment difference between lemborexant 10 mg (LEM10) and PBO on LPS on Day 30 (revised per Amendment 01)
- To evaluate, using PSG, the treatment difference between LEM5 and PBO on sleep efficiency (SE) on Day 30 (revised per Amendment 01)
- To evaluate, using PSG, the treatment difference between LEM10 and PBO on SE on Day 30 (revised per Amendment 01)
- To evaluate safety and tolerability of lemborexant following multiple doses
- To evaluate the pharmacokinetics of lemborexant

Exploratory Objectives

cci [redacted]

Study Design

A multicenter, multiple dose, randomized, double-blind, placebo-controlled, parallel-group study in Korean subjects with insomnia disorder. Subjects will be randomized to LEM5, LEM10 or PBO in a ratio of 2:2:1 and will receive study drug for 30 days.(revised per Amendment 01)

Study Procedures

The study will consist of 2 phases: Prerandomization Phase and 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 28-day Follow-up Period before an End of Study (EOS) Visit.

Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the 1st 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, physical examination, serum pregnancy test (females of childbearing potential only), urine drug test, assessment of suicidality, questioning regarding adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, weight, height, viral screen, clinical hematology, chemistry analysis and urinalysis will be conducted for evaluation of eligibility criteria, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further, that the subject complains of difficulties with sleep onset with or without problems with sleep maintenance and/or awakening earlier in the morning. Screening assessments will include the Insomnia Severity Index (ISI), the Beck Depression Inventory - II (BDI), Beck Anxiety Inventory (BAI), and the Sleep Disorders Screening Battery (SDSB) that consists of STOPBang and International Restless Legs Scale (IRLS).

All eligible subjects will be provided with a paper sleep diary and 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. 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, subjects will undergo the 2nd Screening Visit (Visit 2). This visit must occur between Day –17 and Day –10. On this night on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete sleep diary review for continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. Subjects who continue to meet the eligibility criteria will then prepare check-in for PSG recording. 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). 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 and urine pregnancy test (females of childbearing potential only), and questioning regarding AEs.

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.

Subjects will return to the clinic between Day –10 and Day –5. Subjects who are still eligible will have PSG recording. In the evening, before the PSG recording, the safety assessments including questioning AEs and vital signs assessment will be conducted and a urine drug test and urine

pregnancy test (females of childbearing potential only) will be performed. 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 2nd Screening Visit. Subjects will undergo an 8-hour PSG. The PSG recording will be reviewed for continued eligibility, and it will also provide the baseline values 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. 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.

Baseline and Treatment 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. Subjects will be questioned about study drug compliance. Safety assessments including questioning regarding AEs, 12-lead ECG, vital signs, weight, clinical hematology and chemistry analysis, urinalysis will be conducted. In addition, subjects should undergo a urine drug test and urine pregnancy test (females of childbearing potential only). Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period.

The Treatment Period will begin on Day 1 immediately after the Baseline Period and study drug will be administered before bedtime for the next 30 nights. Subjects will be randomized in a double-blind manner, to receive study drugs, LEM5, LEM10 or PBO.

Study drug will be dispensed to subjects. Subjects will be instructed to take lemborexant or PBO at home in the evening immediately (ie, within 5 minutes) before bedtime on approximately the same schedule as during the Run-in period.

On Day 14, site staff will call subjects to check AEs, concomitant therapy, and drug compliance. In addition, subjects will be reminded to take study drug each night approximately 5 minutes before bedtime and to 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. If any AE is clinically significant and requires follow-up, an unscheduled visit may be arranged per investigator's decision.

On Day 30, subjects will return to the clinic. Subjects will be questioned about study drug compliance and AEs. A urine drug test and urine pregnancy test (females of childbearing potential only) will be performed. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB. A PSG will be conducted at the same time and with the same electrode montage as the PSG during the Run-in Period. On the morning of Day 31, PK samples will be obtained. Safety assessments including questioning regarding AEs, physical examination, 12-lead ECG, vital signs, clinical hematology, chemistry analysis and urinalysis will be conducted. After the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic.

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.

Approximately 28 days after completion of the Treatment Period subjects will return to the clinic for the EOS Visit. At the EOS Visit, in addition to safety assessment including questioning regarding AEs, physical examination, 12-lead ECG, vital signs, clinical hematology, chemistry analysis and urinalysis, a urine drug test and urine pregnancy test (females of childbearing potential

only) will be conducted. After the End of Study 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 at beginning from the time the subject signs the study ICF through the last visit. In addition, subjects who withdraw due to an AE should undergo a urine drug test and urine pregnancy test (females of childbearing potential only).

Additional Study Information

The estimated study duration for each subject on study is anticipated to be a maximum of 93 days 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 58 days. A subject who completes the Treatment Period (assessments through discharge from the clinic on Day 31) will be considered to have completed the study.

Number of Subjects

Approximately 60 Korean subjects with insomnia disorder will be randomized to treatment (LEM5 [24 subjects], LEM10 [24 subjects], and PBO [12 subjects]).(revised per Amendment 01)

Inclusion Criteria

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

1. Korean male or female, age 19 to 80 years, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty getting to sleep with or without difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty staying asleep and/or awakening earlier in the morning, the subject is not eligible)
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Subjective Sleep Onset Latency (sSOL) typically ≥30 minutes on at least 3 nights per week in the previous 4 weeks at Screening
4. ISI score ≥13 at Screening
5. Regular time in bed between 6.5 and 9.0 hours at Screening
6. At 2nd Screening Visit (Visit 2): Confirmation (via Sleep Diary) of a regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 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 09:00 on at least 5 of the final 7 nights
7. Confirmation of current insomnia symptoms, as determined from responses on the sleep diary on the 7 most recent mornings before the PSG during Screening Period (Visit 2), such that sSOL ≥30 minutes on at least 3 of the 7 nights

8. 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 2nd Screening Visit (Visit 2), such that there are no more than 2 nights with time spent in bed duration <7 hours or >10 hours
9. During Run-in period, objective (PSG) evidence of insomnia as follows:
   - SE ≤85%; and
   - LPS ≥30 minutes
10. Provide written informed consent
11. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night

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 [ß-hCG]. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st 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 have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive 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 lifetime suicidal behavior
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. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities
8. Hypersensitivity to lemborexant or to their excipients
9. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
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 (revised per Amendment 01)
    - IRLS ≥16
14. Apnea-Hypopnea Index >15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the 2nd Screening Visit
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 19 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. 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 1st dose of study medication (Run-in Period)
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 1st 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
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 different time zones during the study
28. Performed shift work in the 2 weeks before Screening, or between Screening and Baseline, or plans to do during the study
29. A positive drug test at Screening, Run-in, or Baseline, or unwilling to refrain from use of recreational drugs during the study
30. 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
31. Previously participated in any clinical trial of lemborexant

Study Treatments

Test drug: Lemborexant

LEM5, LEM10 or lemborexant–matched PBO will be orally administered in tablet form approximately 5 minutes before the time the subject intends to try to sleep.

Run-in Period

All subjects will receive 1 tablet of lemborexant–matched PBO for approximately 14 days in a single blind manner during the Run-in Period.

Treatment Period

All subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized:

- LEM5: 1 lemborexant 5 mg tablet for 30 days
- LEM10: 1 lemborexant 10 mg tablet for 30 days
- PBO: 1 lemborexant–matched PBO tablet for 30 days

Duration of Treatment

30 days

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.

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. Subjects must not consume any alcohol on days when they are scheduled for a PSG recording.

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

Prohibited medications include moderate and strong cytochrome P450 (CYP3A) inhibitors and all CYP3A inducers. 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 and all CYP3A inducers will not be permitted at any time for any duration during the study.

Assessments

Screening Assessments

ISI

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

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.

BAI

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.

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

Sleep Diary

The Sleep Diary will be completed each morning within 1 hour after morning wake time from the 1st Screening Visit to the 2nd Screening Visit. This Sleep Diary will yield several self-reported measures of sleep and will be used to determine eligibility at the 2nd Screening Visit.

The following parameters will be collected and calculated from Sleep Diary:

- Bedtime: the time the subject attempts to sleep
- Waketime: the time the subject gets out of bed for the day
- 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 time in bed: time from Bedtime to Waketime

Efficacy Assessments

Polysomnography (PSG)

PSG recordings will be obtained on 1 night between Day –17 and Day –10 during the Screening Period (for the purpose of evaluation of the eligibility criteria), on 1 night between Day –10 and Day –5 during the Run-in Period (to provide baseline PSG parameter values) and the last treatment day (Day 30) of the Treatment Period (to provide post-baseline PSG parameter values). Each PSG will include an electrode montage with electroencephalography (EEG), electromyography, electrooculography, and ECG channels, which permit scoring of sleep architecture via standard sleep scoring criteria. In addition, on the first PSG (during the Screening Period), channels that permit assessment of diagnostic criteria for sleep apnea and periodic limb movements in sleep will be required.

A PSG manual will be provided by the central PSG laboratory.

All PSG parameters will be obtained separately for each PSG at each Period.

The PSG obtained during the Screening period will be used to 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 PSG 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.

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: total sleep time (TST) divided by time spent in bed multiplied by 100
- WASO: minutes of wakefulness from the onset of persistent sleep until lights on
- TST: minutes of sleep from sleep onset until terminal awakening

CCI [redacted]

Pharmacokinetic Assessments

During the Treatment period, blood samples for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be obtained at the prespecified timepoints in the clinic; within

2 hours predose on Day 30; 1 and 1.5 hours after morning waketime on Day 31. The exact time at which PK samples were collected will be recorded. The time and date of the 2 most recent doses preceding the samples obtained on Day 30 will also be documented.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

The efficacy assessments are pharmacodynamic assessments.

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 and ECGs; 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. At telephone visit on Day 14, AE will be confirmed by telephone.

Bioanalytical Methods

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

Statistical Methods

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

Study Endpoints

Primary Endpoint

- Change from baseline of LPS on Day 30 of LEM5 compared to PBO (revised per Amendment 01)

Secondary Endpoints

Efficacy Endpoints

- Change from baseline of LPS on Day 30 of LEM10 compared to PBO (revised per Amendment 01)
- Change from baseline of SE on Day 30 of LEM5 compared to PBO (revised per Amendment 01)
- Change from baseline of SE on Day 30 of LEM10 compared to PBO (revised per Amendment 01)

Safety Endpoint

- Safety and tolerability of lemborexant

Other Endpoint

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

Exploratory Endpoints

CCI

[redacted]

Analysis Sets

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

Full Analysis Set (FAS): The FAS is the group of randomized subjects who received at least 1 dose of randomized study drug and had LPS data from the PSG on Day 30. (revised per Amendment 01)

Per Protocol (PP) Analysis Set: The PP Analysis Set is the FAS who received protocol-assigned study drug and did not have a major protocol deviation that is likely to affect the LPS data of PSG as follows.

- Incorrect study drug kit dispensed
- Study drug not administered
- Prohibited concomitant medication
- Primary efficacy assessment out of window
- Missing primary efficacy assessment
- Duplicate randomization
- Violated inclusion/exclusion criteria

More details of the evaluability criteria will be determined before database lock and will be specified in the SAP. (revised per Amendments 01 and 02)

PK Analysis Set: the PK analysis set is the group of subjects who had at least 1 quantifiable plasma concentration of lemborexant or its metabolites, with adequately documented dosing history.

Efficacy Analyses

The main analysis group for the primary endpoint is the FAS. (revised per Amendment 01) The efficacy analyses will be the pharmacodynamics analyses and it will be performed on the FAS except per protocol analysis will be performed on the PP.

Since LPS is known to be non-normally distributed, the change from baseline to Day 30 of LPS after log-transformation will also be analyzed with analysis of covariance (ANCOVA), comparing PBO and each LEM groups in 1 model, with treatment and baseline (log-transformation) as fixed effects.

The change from baseline to Day 30 of SE will be analyzed with ANCOVA, comparing PBO and each LEM groups in 1 model, with treatment and baseline as fixed effects. The change from baseline to Day 30 of WASO will be analyzed using same statistical method of SE. The each variables and the difference from baseline will be used for summary statistics by each visit and treatments. Data will be plotted as appropriate.

CCI [redacted]

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

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 plasma concentrations of lemborexant and its metabolites M4, M9, and M10 by nominal sampling time and dose.

Pharmacodynamic, Pharmacogenomic, and other Biomarker Analyses

Not applicable.

Safety Analyses

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

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale (revised per Amendment 01)

Sample size was calculated with re-sampling simulation using Study E2006-G000-201 data in order to power the study to detect point estimate of mean difference below a certain threshold with sufficient probability. The certain threshold is defined as –0.44 as derived from the upper limit of 95% CI of pairwise difference between LEM5 and PBO for log(LPS) from Study 201. Using the mean difference to PBO of log(LPS) in LEM5 from the baseline to Days 14/15 from each simulation (10,000 times) that using a grid search and assuming a 2:1 ratio (LEM5:PBO), demonstrated the difference < –0.44 could be achieved with more than 85% power. It is assumed that the mean difference to PBO of log(LPS) in lemborexant groups from baseline to Day 30 in this study will be similar with those from baseline to Days 14/15 in Study 201. When the number of subjects randomized to LEM5 and PBO are 24 and 12, respectively, the number of subjects who complete with evaluable efficacy data will be 22 and 11, respectively. Based on this evaluation, this study will provide power at 88.64% for comparing LEM5 and PBO. Since LEM10 is set as a reference arm, therefore the sample size for LEM10 will be 24 as the same of LEM5 above.

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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
CI	confidence interval
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
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalography
EMG	electromyography
EOS	end of study
ET	early termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation	Term
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
K-GCP	Korean good clinical practice
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
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MHB	median habitual bedtime
NDA	New Drug Application
PBO	placebo
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLMD	periodic limb movement disorder
PP	Per Protocol
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

Abbreviation	Term
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

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 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.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor and the head of the medical institution. The head of the medical institution will inform the early termination/temporary halt of the study by the IRB/IEC to the Ministry of Food and Drug Safety (MFDS) immediately and submit a detailed written explanation of the reasons for the decision.

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

At the end of the study, the sponsor should notify the IRB/IEC and MFDS within the required timeline. The end of the study will be the date of the last study visit for the last subject in the study.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC within the required timeline, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki

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

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the 1st Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

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

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) at approximately 9 investigational sites in South Korea. (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

Insomnia is a common sleep disorder that relies on a patient-reported complaint of difficulty falling asleep and/or difficulty maintaining sleep, ie, frequent awakenings, difficulty returning to sleep after awakenings, or awakening too early with inability to return to sleep (Buysse, 2013). Insomnia is a serious disorder that has deleterious health consequences and impacts a patient's quality of life (DiBonaventura et al, 2015). Untreated insomnia is associated with an increased risk of medical and psychiatric comorbidities, as well as occupational risks, and is associated with significantly increased healthcare services utilization. The annual prevalence of insomnia symptoms in the general adult population in the US is estimated to be from 35% to 50% (Walsh, et al., 2011), and the prevalence of insomnia from 12% to 20% (Morin, et al., 2011; Roth, et al., 2011). In an epidemiology study of insomnia in Korean adult population, 22.8% of subjects complained of insomnia (Cho, et al., 2009).

Currently available pharmacological treatments used clinically for insomnia in Korea include sedative hypnotics (benzodiazepines, non-benzodiazepines GABAergics agents), sedating antidepressants, melatonin, and antihistamines. The analysis report of treatment pattern of insomnia using Health Insurance Review & Assessment Service data reported that in Korea, zolpidem, a non-benzodiazepine, is the most frequently prescribed drug for insomnia as in the US and Japan, and the number of prescriptions of drugs for insomnia continues to increase. However, there are significant limitations with current treatment options. There remains an unmet medical need for a pharmacological treatment with proven efficacy on both sleep onset and sleep maintenance, and with good tolerability and safety, especially in the elderly. Patients need to be able to conduct daily activities without residual sleepiness or cognitive impairment, such as driving and work. Among other serious concerns with available treatments for insomnia are drug-drug and drug-alcohol interactions, abuse liability, and tolerance/habituation effects. Other important safety risks withdrawal symptoms, rebound insomnia, aberrant nocturnal behavior, respiratory depression, and excessive daytime sleepiness.

Orexins have been shown to regulate transitions between wakefulness and sleep by promoting cholinergic/monoaminergic neural pathways, through interaction with two G protein-coupled receptors (OX1R and OX2R). It is suggested that OX1R plays an important role in suppressing the instigation of non-REM sleep, while OX2R has a major role in promoting wakefulness. The activation of the orexinergic system promotes wakefulness, and its disruption brings about sleep disturbances. Thus, it was thought that antagonising the orexin system during the night might reduce excessive wakefulness, and improve sleep continuity (Equihua, et al., 2013). This has now been demonstrated with several members of the dual orexin receptor antagonist (DORA) class, such as the approval of suvorexant and lemborexant in several countries including the US and Japan.

7.1 Compound overview

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. Lemborexant is competitive dual antagonist of orexin-1 (OX1R) and orexin-2 (OX2R) receptors, with higher affinity for OX2R.

Lemborexant was approved in the US on 20 December 2019 for the treatment of insomnia in adult patients, characterized by difficulties with sleep onset and/or sleep maintenance and in Japan on 23 January 2020 for the treatment of insomnia in adult patients. In addition, lemborexant was approved in some other countries for the treatment of insomnia in adult patients.

7.2 Clinical Experience

7.2.1 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-A001-008 (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. Lemborexant 2.5, LEM5 and LEM10 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.

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, LEM5, 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.

7.2.2 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 sleep efficiency (SE) was achieved without unacceptable next-day residual sleepiness as evaluated by the Karolinska Sleepiness Scale (KSS).

As measured by PSG, improvements in sleep were also demonstrated by statistically significant increases from baseline in SE, and by decreases from baseline in mean latency to persistet sleep (LPS) and wake after sleep onset (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.

7.2.3 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 subjective sleep onset latency (sSOL), subjective sleep efficiency (sSE), subjective wake after sleep onset (sWASO), and subjective total sleep time (sTST), over the first 7 nights and the last 7 nights of treatment.

E2006-G000-303 (Study 303): Study 303 was a 12-month 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. During the first 6 months (Period 1), subjects were randomized to PBO, LEM5, or LEM10. During the second 6 months (Period 2), LEM subjects continued their assigned dose, but PBO subjects were rerandomized to LEM5 or 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. The efficacy of LEM at 6 months of treatment persisted at 12 months. LEM was well tolerated over 12 months.

The clinical development program established the safety, tolerability, and efficacy (both short- and long-term) of lemborexant versus PBO in adult and older adult subjects. In addition, there was no evidence for tolerance or dependence or for rebound insomnia.

7.3 Study Rationale

According to the Guideline for bridging data issued by National Institute of Food and Drug Safety Evaluation (Dec, 2015) and the relevant regulation in Korea, for the new drug application of lemborexant in South Korea, a bridging study is required to show the comparability of pharmacodynamic profile of lemborexant between Korean and non-Korean subjects to be able to extrapolate overseas clinical data of lemborexant to Korean population. Therefore, this study is designed to be combine components of dose-response study E2006-G000-201 (Study 201) with respect to ages of the patient population as well as Study 304 with respect to duration of study and doses of lemborexant. These components are based on the recommendations of MFDS.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate, using polysomnography (PSG), the treatment difference between lemborexant 5 mg (LEM5) and placebo (PBO) on latency to persistent sleep (LPS) on Day 30. (revised per Amendment 01)

8.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate, using PSG, the treatment difference between lemborexant 10 mg (LEM10) and PBO on LPS on Day 30 (revised per Amendment 01)
- To evaluate, using PSG, the treatment difference between LEM5 and PBO on sleep efficiency (SE) on Day 30 (revised per Amendment 01)
- To evaluate, using PSG, the treatment difference between LEM10 and PBO on SE on Day 30 (revised per Amendment 01)
- To evaluate safety and tolerability of lemborexant following multiple doses (revised per Amendment 01)
- To evaluate the pharmacokinetics of lemborexant

8.3 Exploratory Objectives

CCI [redacted]

CCI [redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a multicenter, multiple dose, randomized, double-blind, placebo-controlled, parallel-group study in Korean subjects with insomnia disorder. Subjects will be randomized to LEM5, LEM10 or PBO in a ratio of 2:2:1 and will receive study drug for 30 days.(revised per Amendment 01)

The study will consist of 2 phases: Prerandomization Phase and 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 28-day Follow-up Period before an End of Study (EOS) Visit.

The estimated study duration for each subject on study is anticipated to be a maximum of 93 days 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 58 days. A subject who completes the Treatment Period (assessments through discharge from the clinic on Day 31) will be considered to have completed the study.

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

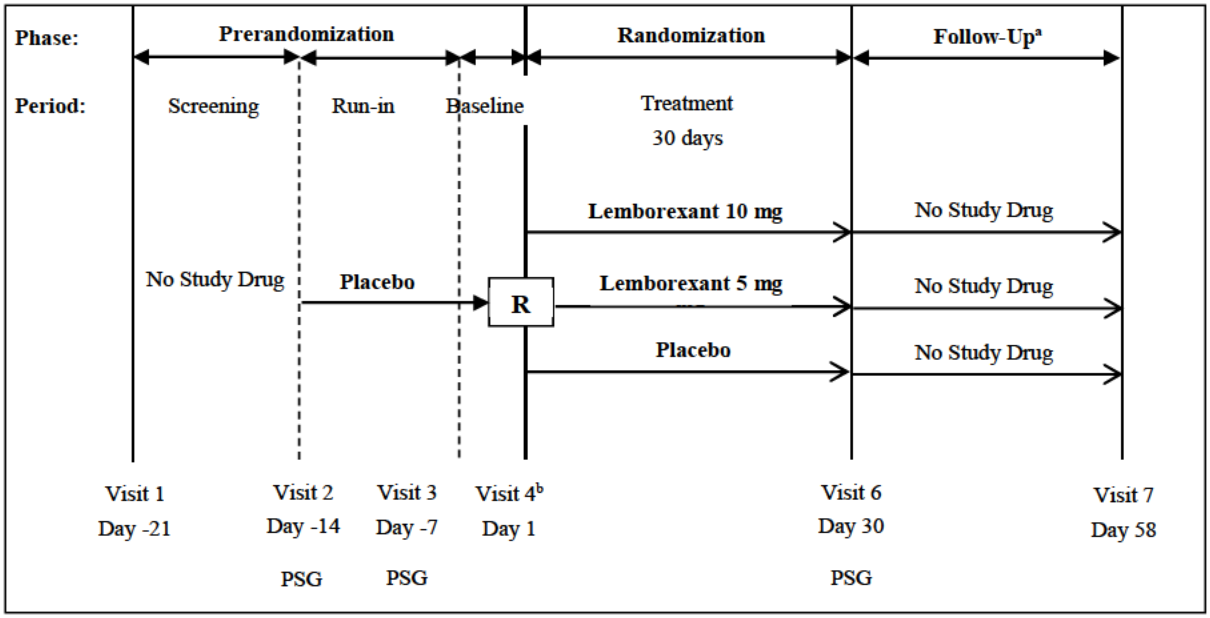

Figure 1 Schematic Diagram of E2006-J082-204 Study Design

PSG = polysomnography, R = randomization

a: a minimum 28-day Follow-up

b: On Day 1 (at Visit 4), the Run-in Period will end and the Baseline Period will begin. The Treatment Period will begin on Day 1 immediately after the Baseline Period as study drug will be administered before bedtime

9.1.1 Prerandomization 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.

9.1.1.1 Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the 1st 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, physical examination, serum pregnancy test (females of childbearing potential only), urine drug test, assessment of suicidality, questioning regarding adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, weight, height, viral screen, clinical hematology, chemistry analysis and urinalysis will be conducted for evaluation of eligibility criteria, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further, that the subject complains of difficulties with sleep onset with or without problems with sleep maintenance and/or awakening earlier in the morning. Screening assessments will include the Insomnia Severity Index (ISI), the Beck Depression Inventory - II (BDI), Beck Anxiety Inventory (BAI), and the Sleep Disorders Screening Battery (SDSB) that consists of STOPBang and International Restless Legs Scale (IRLS).

All eligible subjects will be provided with a paper sleep diary and 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. 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, subjects will undergo the 2nd Screening Visit (Visit 2). This visit must occur between Day –17 and Day –10. On this night on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete sleep diary review for continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. Subjects who continue to meet the eligibility criteria will then prepare check-in for PSG recording. 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). 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 and urine pregnancy test (females of childbearing potential only), and questioning regarding AEs.

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.

Subjects will return to the clinic between Day –10 and Day –5. Subjects who are still eligible will have PSG recording. In the evening, before the PSG recording, the safety assessments including questioning AEs and vital signs assessment will be conducted and urine drug test and urine pregnancy test (females of childbearing potential only) will be performed. 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 2nd Screening Visit. Subjects will undergo an 8-hour PSG. The PSG recording will be reviewed for continued eligibility, and it will also provide the baseline values 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. 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.

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. Subjects will be questioned about study drug compliance. Safety assessments including questioning regarding AEs, 12-lead ECG, vital signs, weight, clinical hematology and chemistry analysis, urinalysis will be conducted. In addition, subjects should undergo a urine drug test and urine pregnancy test (females of childbearing potential only).

9.1.2 Randomization Phase

The Randomization Phase will comprise a Treatment Period during which subjects will be treated for 30 nights, and a minimum 28-day Follow-up Period before an End of Study (EOS) Visit.

9.1.2.1 Treatment Period

Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period.

The Treatment Period will begin on Day 1 immediately after the Baseline Period and study drug will be administered for the next 30 nights. Subjects will be randomized in a double-blind manner, to receive study drugs, LEM5, LEM10 or PBO.

Study drug will be dispensed to subjects. Subjects will be instructed to take lemborexant or PBO at home in the evening immediately (ie, within 5 minutes) before bedtime on approximately the same schedule as during the Run-in period.

On Day 14, site staff will call subjects to check AEs, concomitant therapy, and drug compliance. In addition, subjects will be reminded to take study drug each night approximately 5 minutes before bedtime and to 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. If any AE is clinically significant and requires follow-up, an unscheduled visit may be arranged per investigator's decision.

On Day 30, subjects will return to the clinic. Subjects will be questioned about study drug compliance and AEs. A urine drug test and urine pregnancy test (females of childbearing potential only) will be performed. A PK blood sample will be collected predose and study drug will be administered approximately 5 minutes before the subject's MHB. A PSG will be conducted at the same time and with the same electrode montage as the PSG during the Run-In Period. On the morning of Day 31, PK samples will be obtained. Safety assessments including questioning regarding AEs, physical examination, 12-lead ECG, vital signs, clinical hematology, chemistry analysis and urinalysis will be conducted. After the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic.

9.1.2.2 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.

Approximately 28 days after completion of the Treatment Period subjects will return to the clinic for the EOS Visit. At the EOS Visit, in addition to safety assessments including questioning regarding AEs, physical examination, 12-lead ECG, vital signs, clinical hematology, chemistry analysis and urinalysis, a urine drug test and urine pregnancy test (females of childbearing potential only) will be conducted. After the End of Study Visit, subjects' participation in the study will be finished.

9.1.2.3 Additional study information

The estimated study duration for each subject on study is anticipated to be a maximum of 93 days 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 58 days. A subject who completes the Treatment Period (assessments through discharge from the clinic on Day 31) will be considered to have completed the study.

9.1.2.4 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 at beginning from the time the subject signs the study ICF through the last visit. In addition, subjects who withdraw due to an AE should undergo a urine drug test and urine pregnancy test (females of childbearing potential only).

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 that would render them unable to meet inclusion criteria.

The Run-in Period will also help to identify and exclude subjects who are not compliant with the duration of time spent in bed, or restrictions on alcohol and caffeine use. In this regard, it is necessary for the subjects to be taking PBO. After this minimum 7 nights of treatment, eligible subjects will have PSG recording at Visit 3. These recordings will be used to further screen for eligibility, and will serve as baseline values for those subjects who continue to randomization.

9.2.3 Pharmacodynamic Parameters

Sleep parameters measured by PSG are selected as the Pharmacodynamic (PD) parameters. PSG involves simultaneous recording of several electrophysiological parameters (such as electroencephalogram) to provide objective measures of physiologic changes that are characteristic of the different sleep stages as well as improvement in measurements of sleep onset and sleep maintenance. Therefore, sleep parameters measured by PSG are both PD endpoints and efficacy endpoints.

9.2.4 Study Duration

In Study 201, treatment benefit of LEM5 was demonstrated at the end of treatment on Days 14/15, however, based on the regulatory advice, 2 weeks of treatment duration are not sufficient. (revised per Amendment 01) As the result from Study 304 showed that lemborexant effects measured by PSG observed at the start of treatment were maintained at 1 month, thus the study duration is based on Study 304.

9.3 Selection of Study Population

Approximately 60 subjects in South Korea will be randomized to treatment (LEM5 [24 subjects], LEM10 [24 subjects], and PBO [12 subjects]). (revised per Amendment 01) The eligibility criteria are based on Study 201. 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. Korean male or female, age 19 to 80 years, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty getting to sleep with or without 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. Subjective Sleep Onset Latency (sSOL) typically ≥30 minutes on at least 3 nights per week in the previous 4 weeks at Screening
4. ISI score ≥13 at Screening
5. Regular time in bed between 6.5 and 9.0 hours at Screening
6. At 2nd Screening Visit (Visit 2): Confirmation (via Sleep Diary) of a regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 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 09:00 on at least 5 of the final 7 nights.
7. Confirmation of current insomnia symptoms, as determined from responses on the sleep diary on the 7 most recent mornings before the PSG during Screening Period (Visit 2), such that sSOL ≥30 minutes on at least 3 of the 7 nights
8. 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 2nd Screening Visit (Visit 2), such that there are no more than 2 nights with time spent in bed duration <7 hours or >10 hours
9. During Run-in period, objective (PSG) evidence of insomnia as follows:
   - SE ≤85%; and
   - LPS ≥30 minutes
10. Provide written informed consent
11. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night

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 [ß-hCG]. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st 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 have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive 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 lifetime suicidal behavior
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. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities
8. Hypersensitivity to lemborexant or to their excipients
9. Scheduled for surgery during the study that requires general anesthesia or administration of prohibited medications
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 (revised per Amendment 01)
    - IRLS ≥16

14. Apnea-Hypopnea Index >15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the 2nd Screening Visit
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 19 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. 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 1st dose of study medication (Run-in Period).
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 1st 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

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 different time zones during the study
28. Performed shift work in the 2 weeks before Screening, or between Screening and Baseline, or plans to do during the study
29. A positive drug test at Screening, Run-in, or Baseline, or unwilling to refrain from use of recreational drugs during the study
30. 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
31. Previously participated in any clinical trial of lemborexant

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

A subject who discontinues study treatment should return for an early termination (ET) Visit as soon as possible and will complete End-of-Study procedures (see Section 9.5.5). The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition electronic case report form (eCRF). In addition, the date of last dose of study drug(s) will be recorded.

9.4 Treatments

9.4.1 Treatments Administered

Test drug

LEM5, 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.

Run-In Period

All subjects will receive 1 tablet of lemborexant-matched PBO for approximately 14 days 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

All subjects will receive 1 tablet as described below approximately 5 minutes before the time the subject intends to try to sleep, according to the treatment arm to which the subject has been randomized:

- LEM5: 1 lemborexant 5 mg tablet for 30 days
- LEM10: 1 lemborexant 10 mg tablet for 30 days

- PBO: 1 lemborexant-matched PBO tablet for 30 days

9.4.2 Identity of Investigational Products

The sponsor will provide lemborexant tablets in strengths of 5, and 10 mg and lemborexant-matched PBO, identical in appearance. Tablets will be packaged in blister cards in a double-blind manner.

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.

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

9.4.2.3 Labeling for Study Drug

Lemborexant will be labeled in accordance with text in Korean that is in full regulatory compliance with South Korea.

The following information has to be provided:

- For clinical study use only
- Name, address, and contact number of the sponsor
- Chemical name/drug identifier (in case of a blind study, to write side by side both active drug and comparator drug)
- Lot number/batch number
- Storage conditions, expiration date
- Keep out of sight and reach of children
- Reference code that can identify a clinical study
- Others according to the relevant regulation

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 is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments 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.

After the Baseline Period on Day 1, subjects will be randomized, in a double-blind manner, to receive either LEM5, LEM10 or PBO in a 2:2:1 ratio on Day 1 using a centralized randomization technique. (revised per Amendments 01 and 02)

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 Baseline Period on Day 1), the investigator or designee will call the IxRS to register the subject information. At randomization (after the Baseline Period on Day 1), the IxRS will assign each subject a unique 6-digit randomization number.

9.4.4 Selection of Doses in the Study

The approved doses in the US and Japan, which is lemborexant 5 mg and 10 mg per day, are selected to assess pharmacodynamic profile of lemborexant in Korean subjects.

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 interactive voice and web response system (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 at the date of informed consent, will be recorded on the Prior and Concomitant Medication 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 drug (Run-in Period).

Prohibited medications include moderate and strong CYP3A inhibitors and all CYP3A inducers. 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 and all CYP3A inducers will not be permitted at any time for any duration of use during the study.

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.

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. Subjects must not consume any alcohol on days when they are scheduled for a PSG recording.

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.

When subjects visit site for Baseline assessment, 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 and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local requirements.

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

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening Assessments

9.5.1.1.1 DEMOGRAPHY

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

9.5.1.1.2 MEDICAL HISTORY, PSYCHIATRIC 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.

Physical examinations (full or brief) will be performed as described in Section 9.5.1.4.5.

9.5.1.1.3 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.

Screening battery will include the Insomnia Severity Index (ISI), the Beck Depression Inventory - II (BDI-II), Beck Anxiety Inventory (BAI), and the Sleep Disorders Screening Battery (SDSB) that consists of STOPBang and International Restless Legs Scale (IRLS).

ISI

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.

BDI-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 (Beck et al., 1961). Scores on the BDI-II range from 0 to 63, with higher scores indicating higher levels of depressive symptoms.

BAI

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 (Beck et al., 1988). Scores on the BAI range from 0 to 63, with higher scores indicating higher levels of anxiety symptoms.

SDSB

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: a subjective scale comprising ten questions, which measures severity of symptoms of restless legs syndrome (Abetz et al., 2006)

Sleep Diary

The paper sleep diary will be completed each morning within 1 hour after morning wake time from the 1st Screening Visit to the 2nd Screening Visit. This Sleep Diary will yield several self-reported measures of sleep and will be used to determine eligibility at the 2nd Screening Visit.

The following parameters will be collected and calculated from Sleep Diary:

- Bedtime: the time the subject attempts to sleep
- Waketime: the time the subject gets out of bed for the day
- 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 time in bed: time from Bedtime to Waketime

9.5.1.1.4 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). A dipstick will be used for urine pregnancy testing.

9.5.1.1.5 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 Efficacy Assessments

9.5.1.2.1 POLYSOMNOGRAPHY

Each PSG will include an electrode montage with electroencephalography (EEG), electromyography, electrooculography, and ECG channels, which permit scoring of sleep architecture via standard sleep scoring criteria. In addition, on the first PSG (during the Screening Period), channels that permit assessment of diagnostic criteria for sleep apnea and periodic limb movements in sleep will be required.

A PSG manual will be provided by the central PSG laboratory.

All PSG parameters will be obtained separately for each PSG at each Period.

Trained PSG scorers will score PSG records in 30-second epochs according to standard criteria. The PSG obtained during the Screening period will be used to only to calculate the Apnea-Hypopnea Index and the Periodic Limb Movements with Arousal Index for evaluation of the eligibility criteria; sleep parameters and sleep architecture will not be evaluated from this PSG. The PSG obtained during the Run-in period will be used to a) determine eligibility and b) provide baseline PSG parameter values for those subjects who are randomized. The PSG obtained on the last treatment day (Day 30) of the Treatment Period will be used to provide post-baseline PSG parameter values.

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: total sleep time (TST) divided by time spent in bed multiplied by 100
- WASO: minutes of wakefulness from the onset of persistent sleep until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- CCI [redacted]

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

During the Treatment period, a single blood samples (4 mL per blood draw) for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be obtained at the prespecified timepoints in the clinic; within 2 hours predose on Day 30; 1 and 1.5 hours (1 hour and 30 minutes) after morning waketime on Day 31. The exact time at which PK samples were collected will be recorded. The time and date of the 2 most recent doses preceding the samples obtained on Day 30 will also 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. (revised per Amendment 02)

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Not applicable.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in Table 3. 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. At telephone visit on Day 14, AE will be confirmed by telephone.

9.5.1.4.1 ADVERSE EVENTS

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

The criteria for identifying AEs in this study are:

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

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit. Refer to Section 9.5.4.1 for the time period after the end of treatment for SAE collection.

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

laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) 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 and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

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

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

Assessing Severity of Adverse Events

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

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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.4.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

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

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

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

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

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.4.3 LABORATORY MEASUREMENTS

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 3. Subjects should be in a seated or supine position during blood collection.

The total blood volume to be drawn for laboratory measures in the study (Table 2) will be indicated on the ICF.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	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.

Table 2 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments

	Volume[a] per Sample Collection (mL)	Collection Time points	Window Around Time Point	Total Volume[a] Collected (mL)
Clinical laboratory tests[b]	7 (revised per Amendment 02)	Screening Day 1 Day 31 End of Study	n/a	28 (revised per Amendment 02)

Table 2 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments

	Volume[a] per Sample Collection (mL)	Collection Time points	Window Around Time Point	Total Volume[a] Collected (mL)
Pregnancy testing[c] (revised per Amendment 02)	n/a (revised per Amendment 02)	Screening	n/a	n/a (revised per Amendment 02)
Viral tests	8.5 (revised per Amendment 02)	Screening	n/a	8.5 (revised per Amendment 02)
Pharmacokinetic sampling (revised per Amendment 02)	4	Day 30 (1 time within 2 hours predose), Day 31 (2 times; 1 and 1.5 hours after morning waketime) (revised per Amendment 02)	+/– 15 mins	12
Total				48.5 mL (revised per Amendment 02)

n/a: not applicable
a: Estimated volume.
b: Clinical laboratory tests will also be conducted at ET visits, and may also be obtained at unscheduled visits at the discretion of the investigator.
c: Included in the clinical laboratory test volume (revised per Amendment 02)

With the exception of assessing for bacteria in urine tests, clinical laboratory assessments during the study will be performed by a central laboratory. During the study, bacteria in urinalysis will be performed by a local laboratory of each site (revised per Amendment 03). All blood samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. Urine samples will be collected, and the split samples will be sent to both the central laboratory and the local laboratory on the day of collection unless otherwise instructed (revised per Amendment 03). 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.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF (see Section 9.5.4.3.2).

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]) will be obtained at the visits designated in 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.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations (full or brief) will be performed as designated in the Schedule of Procedures/Assessments (Table 3). At Screening and at the end-of study (EOS) visit, a comprehensive physical examination will be conducted, including evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. 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 examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

9.5.1.4.6 ELECTROCARDIOGRAMS

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

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

9.5.1.4.7 OTHER SAFETY ASSESSMENTS

Urine Drug Test

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. A dipstick will be used for urine drug testing.

9.5.1.5 Other 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 the study.

Table 3 Schedule of Procedures/Assessments in Study E2006-J082-204:

Phase	**Prerandomization**						**Randomization**						
Period	**Screening**			**Run-in**		**Baseline**	**Treatment**				**Follo w-up**	**EOS /ET[b]**	**UNS**
Visit	**1[a]**	**2a**	**2b[a]**	**3a**	**3b**	**4**		**5[j]**	**6a**	**6b**	**NA**	**7**	
Day(s)	**−21**	**−14**	**−13**	**−7**	**−6**	**1**	**1[c]**	**14**	**30**	**31**	**32-57**	**58**	
Visit window	**−14/+4**	**−3/+4**		**−3/+2**		**NA**	**NA**	**−2/+2**	**−2/+5**		**NA**	**+4**	
Assessments													
Demography	X												
Informed Consent	X												
Inclusion/Exclusion criteria	---------->												
Medical/psychiatric/ sleep history	X												
Comprehensive physical exam	X											X	
Brief physical exam										X			X
Beck Depression Inventory - II	X												
Beck Anxiety Inventory	X												
SDSB	X												
Serum pregnancy test	X												
Urine pregnancy test[d]		X		X		X			X			X	X
Urine drug test[d]	X	X		X		X			X			X	
Insomnia Severity Index	X												
Sleep Diary[e]	---------->												
Height	X												
Weight	X					X				X		X	
Viral screen (HCVAb, HBsAg)	X												

Phase	**Prerandomization**						**Randomization**						
Period	**Screening**			**Run-in**		**Baseline**	**Treatment**				**Follow-up**	**EOS /ET[b]**	**UNS**
Visit	**1[a]**	**2a**	**2b[a]**	**3a**	**3b**	**4**		**5[j]**	**6a**	**6b**	**NA**	**7**	
Day(s)	**−21**	**−14**	**−13**	**−7**	**−6**	**1**	**1[c]**	**14**	**30**	**31**	**32-57**	**58**	
Visit window	**−14/+4**	**−3/+4**		**−3/+2**		**NA**	**NA**	**−2/+2**	**−2/+5**		**NA**	**+4**	
Assessments													
Clinical laboratory tests	X					X				X		X	X
Vital signs	X			X		X				X		X	X
PK blood sampling[f]									X	X			
12-lead ECG	X					X				X		X	X
PSG[g]		X		X					X				
Randomization						X							
Dispense study drug			X				X						
Study drug administration[h]				----------					---------->				
Retrieve unused study drug						X			X				
Check study drug compliance[i]				X		X			X				
Admission to clinic		X		X					X				
Discharge from clinic			X		X					X			
Discharge from study												X	
Adverse events	<----------												---------->
Prior and concomitant medication	<----------												---------->

ECG = electrocardiogram, EEG = electroencephalography, EMG =electromyogram, EOG = electro-oculogram, EOS = end of study, ET = early termination, h = hour(s), HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HIV = human immunodeficiency virus, NA = Not applicable, PK = pharmacokinetic, PSG = polysomnography, SDSB = Sleep Disorders Screening Battery, UNS = Unscheduled Visit.

a. Eligible subjects will be scheduled for screening and baseline PSGs.

b. Any subject who early terminates will complete End-of-Study procedures.

c. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized and will begin the Treatment Period.

d. A dipstick will be used for urine pregnancy testing and urine drug testing at the prespecified time points.

e. Should be completed, within 1 hour of morning waketime, on every day of the study from Visit 1 to Visit 2 and reviewed for eligibility before initiating any study assessments at Visit 2.

f. Blood samples (4 mL) will be obtained at the following timepoints: within 2 hours predose on Day 30; 1 and 1.5 hours (1 hour and 30 minutes) after morning waketime on Day 31. (revised per Amendments 01 and 02)

g. PSG recordings will include a standard montage on all PSG nights (EEG, EMG, EOG, ECG). Diagnostic channels (respiratory effort, airflow, and leg EMG) will be added to the standard montage on the PSG at Visit 2.

h. First dose of study drug (PBO) will be taken by the subject on the 1st night at home after Visit 2. On the days that subjects were admitted to the clinic, study drug will be administered to the subject by clinical staff. The 1st dose of active study drug will be taken by the subject on the evening following Visit 3. On days that the subjects are not admitted to the clinic, subjects self-administer study drug. All study drug administration must be within 5 minutes of bedtime (defined as the time the subject attempted to sleep).

i. Subjects will be questioned about study drug compliance upon check-in at Visits 3, 4 and 6. Tablet counts for study drug compliance will be done after end of Run-in Period and end of Treatment Period.

j. On Day 14, site staff will call subjects to check AEs, concomitant therapy, and drug compliance. In addition, subject will be reminded to take study drug each night approximately 5 minutes before bedtime and to 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. If any AE is clinically significant and requires follow-up, an unscheduled visit may be arranged per investigator's decision.

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

All clinical assessments are standard measurements commonly used in studies of insomnia disorder.

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

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

9.5.4.1 Reporting of Serious Adverse Events

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

Serious adverse events, regardless of causality assessment, must be collected 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 relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours 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 Associated with Special Situations

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

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in 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 CRF.

9.5.4.3.2 Reporting of Abnormal hepatic Tests of Clinical Interest

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

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

  AND

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

  AND AT THE SAME TIME

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

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

9.5.4.3.3 Reporting of Study-Specific Events

Not applicable.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within

specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

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

9.5.4.6 Regulatory Reporting of Adverse Events

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

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early termination procedures indicated in the Schedule of Procedures/Assessments (Table 3).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow up, subject choice, 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 secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may 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 9.5.1.4.1. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

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

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding and a snapshot of the database is obtained 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 SAP.

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint will be change from baseline of LPS on Day 30 of LEM5 compared to PBO. (revised per Amendment 01)

9.7.1.1.2 SECONDARY ENDPOINTS

Efficacy Endpoints

- Change from baseline of LPS on Day 30 of LEM10 compared to PBO (revised per Amendment 01)
- Change from baseline of SE on Day 30 of LEM5 compared to PBO (revised per Amendment 01)
- Change from baseline of SE on Day 30 of LEM10 compared to PBO (revised per Amendment 01)

Safety Endpoints

- Safety and tolerability of lemborexant

Other Endpoint

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

9.7.1.1.3 EXPLORATORY ENDPOINTS

Efficacy Endpoints

CCI [redacted]

CCI

[redacted]

9.7.1.2 Definitions of Analysis Sets

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

Full Analysis Set (FAS): The FAS is the group of randomized subjects who received at least 1 dose of randomized study drug and had LPS data from the PSG on Day 30. (revised per Amendment 01)

Per Protocol (PP) Analysis Set: The PP Analysis Set is the FAS who received protocol-assigned study drug and did not have a major protocol deviation that is likely to affect the LPS data of PSG as follows.

- Incorrect study drug kit dispensed
- Study drug not administered
- Prohibited concomitant medication
- Primary efficacy assessment out of window
- Missing primary efficacy assessment
- Duplicate randomization
- Violated inclusion/exclusion criteria

More details of the evaluability criteria will be determined before database lock and will be specified in the SAP. (revised per Amendments 01 and 02)

PK Analysis Set: The PK analysis set is the group of subjects who had at least 1 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 and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and body mass index (BMI); categorical variables include sex, age group, BMI group, and race.

Characteristics of insomnia at Study Baseline will be summarized using LPS, SE, WASO, and ISI.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (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 will be defined as medications that stopped before the first dose of study drug where study drug includes PBO during the Run-in Period.

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The main analysis group for the primary endpoint is the FAS. (revised per Amendment 01) The efficacy analyses will be performed on the FAS except per protocol analysis will be performed on the PP. The each variables and the difference from baseline will be used for summary statistics by each visit and treatments. Data will be plotted as appropriate.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Since LPS is known to be non-normally distributed, the change from baseline to Day 30 of LPS after log-transformation for each will also be analyzed with analysis of covariance (ANCOVA), with treatment and baseline (log-transformation) as fixed effects.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The change from baseline to Day 30 of SE will be analyzed with ANCOVA, with treatment and baseline as fixed effects.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

CCI [redacted]

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 plasma concentrations of lemborexant and its metabolites M4, M9, and M10 by nominal sampling time and dose.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

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 for each study drug.

Compliance for each study drug 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 greater than 120%.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 23.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

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

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

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

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

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

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

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

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

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

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

9.7.1.8.4 VITAL SIGNS AND WEIGHT

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

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

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

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable.

9.7.2 Determination of Sample Size

Sample size was calculated with re-sampling simulation using Study E2006-G000-201 data in order to power the study to detect point estimate of mean difference below a certain threshold with sufficient probability. The certain threshold is defined as –0.44 as derived from the upper limit of 95% CI of pairwise difference between LEM5 and PBO for log(LPS) from Study 201. Using the mean difference to PBO of log(LPS) in LEM5 from the baseline to Days 14/15 from each simulation (10,000 times) that using a grid search and assuming a 2:1 ratio (LEM5:PBO), demonstrated the difference < –0.44 could be achieved with more than 85% power. It is assumed that the mean difference to PBO of log(LPS) in lemborexant groups from baseline to Day 30 in this study will be similar with those from baseline to Days 14/15 in Study 201. When the number of subjects randomized to LEM5 and PBO are 24 and 12, respectively, the number of subjects who complete with evaluable efficacy data will be 22 and 11, respectively. Based on this evaluation, this study will provide power at 88.64% for comparing LEM5 and PBO. Since LEM10 is set as a reference arm, therefore the sample size for LEM10 will be 24 as the same of LEM5 above. (revised per Amendment 01)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

10 REFERENCE LIST

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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 (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes 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, polysomnographs) regardless of how these images are stored, including microfiche and photographic negatives
- Medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

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

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

11.5 Identification of Source Data

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents, Investigator and Site Information Form. 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.

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

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor 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

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	N/A
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	N/A
Alkaline phosphatase	>ULN – 2.5×ULN	>2.5 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULNl	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 - 3.0×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	>2.5 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L;	>500 mg/dL; >27.8 mmol/L;
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
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	N/A	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L;	>155 – 160 mmol/L	>160 mmol/L
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L
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
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L	N/A	N/A	>10 mg/dL >0.59 mmol/L

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.

(revised per Amendments 01 and 02)

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.

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, 9	None
Exclusion Criterion Number	1 – 30	1, 20, 21, 22, 23, 24, 25, 27, 28, 29	1, 9, 20, 21, 22, 27, 28, 29

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
Antidepressants with known sedating effects	Amitriptyline Clomipramine Desipramine Doxepin Imipramine Mirtazapine Nefazodone Nortriptyline Protriptyline (revised per Amendment 01) Trazodone Trimipramine
Antihistamines (centrally-acting H1, including over the counter)	Diphenhydramine HCl Carbinoxamine Doxylamine Dimenhyrinate Triprolidine Bromopheniramine Chlorphemamine Hydroxazine
Antihistamines with known sedating effects	*Non-sedating, eg, loratadine is not prohibited*
Anxiolytics with known sedating effects	Lorazepam Alprazolam Buspirone
Moderate CYP3A inhibitors	Aprepitant Ciprofloxacin Conivaptan Crizotinib

Category	Medication
	Cyclosporine Diltiazem Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Tofisopam Verapamil
Strong CYP3A inhibitors	Boceprevir Clarithromycin Cobicistat Danoprevir and ritonavir Elvitegravir and ritonavir Grapefruit juice Idelalisib Indinavir and ritonavir Itraconazole Ketoconazole Lopinavir and ritonavir Nefazodone Nelfinavir Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) Posaconazole Ritonavir Saquinavir and ritonavir Telaprevir Tipranavir and ritonavir Telithromycin Troleandomycin Voriconazole
CYP3A inducers	Apalutamide Armodafinil Bosentan Carbamazepine Efavirenz Enzalutamide

Category	Medication
	Etravirine Mitotane Modafinil Phenytoin Rifampin Rufinamide St. John's wort Phenobarbital Primidone
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	Tranylcypromine (revised per Amendment 01) Phenelzine (revised per Amendment 01) Isocarboxazid. (revised per Amendment 01)
Norepinephrine and dopamine reuptake inhibitors (NDRIs)	Bupuropion (revised per Amendment 01)
Opioid Analgesics	–
Muscle relaxants (centrally-acting) with known sedating effects	GABA analogues Hydantoins Phenyltriazines
Stimulants	Amphetamines Modafinil Armodafinil Methylfenidate

Category	Medication
Other	Warfarin, heparin, ticlopidine Non-stimulant diet pills Systemic isoretinoin Systemic glucocorticoids Tryptophan

SPONSOR SIGNATURE PAGE

Study Protocol Number:	E2006-J082-204
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Assess the Pharmacodynamics of Lemborexant in Korean Subjects with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant

Chief Portfolio Officer, Eisai Co., Ltd.	Signature	Date

INVESTIGATOR SIGNATURE PAGE

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Investigational Product Name:	E2006/lemborexant

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

Medical Institution

Investigator	Signature	Date