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Clinical Study Protocol

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	E2006/lemborexant
Indication:	Insomnia
Phase:	3
Approval Date:	V1.0 21 Mar 2016 (original protocol)
IND Number:	111,871
EudraCT Number:	2015-004347-39
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder

Investigator(s)

To be determined

Site(s)

Approximately 90 sites in North America and Europe

Study Period and Phase of Development

Approximately 64 weeks

Phase 3

Objectives

Primary Objective

Demonstrate using polysomnography (PSG) that 10 mg lemborexant (LEM10) is superior to zolpidem tartrate extended release 6.25 mg (Ambien CR®; ZOL) on objective sleep maintenance as assessed by wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder

Key Secondary Objectives

- Demonstrate that 5 mg lemborexant (LEM5) is superior to ZOL on objective sleep maintenance as assessed by WASO2H after the last 2 nights of treatment
- Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment

Additional Secondary Objectives

- Compare the efficacy of LEM5 and LEM10 to ZOL on other PSG variables (latency to persistent sleep [LPS], sleep efficiency [SE], wake after sleep onset [WASO], and total sleep time [TST]) after the first 2 nights and the last 2 nights of treatment and on Sleep Diary variables (subjective sleep onset latency [sSOL], subjective sleep efficiency [sSE], subjective wake after sleep onset [sWASO], and subjective TST [sTST]) over the first 7 nights and the last 7 nights of treatment.
- Confirm the efficacy of LEM5 and LEM10 compared to placebo (PBO) on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary sSOL and sWASO
- Evaluate the safety and tolerability of lemborexant
- Compare the efficacy of LEM5 and LEM10 to ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) at the end of treatment
- Compare the safety of LEM5 and LEM10 to ZOL and PBO on cognitive performance in the morning after the first 2 nights of treatment

Exploratory Objectives

- Explore the effects of LEM5, LEM10, ZOL and PBO on:
  - Subjective quality of sleep
  - Postural stability in the morning after the last 2 nights of treatment
  - Cognitive performance after the last 2 nights of treatment
  - Rebound insomnia in the 2 weeks following 30 days of treatment
  - Subjective ratings of morning sleepiness during and following completion of treatment
  - Sleep architecture parameters and other PSG variables
  - Health outcomes on the Patient Global Impression - Insomnia (PGI-Insomnia) and EQ-5D-3L
  - Withdrawal symptoms after completion of treatment
- Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Conduct population pharmacokinetic (PK) modeling for lemborexant
- Explore PK/pharmacodynamic (PK/PD) relationships between lemborexant concentrations and efficacy and safety variables

Study Design

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males 65 years or older or females 55 years or older. At least 60% of the subjects will be age 65 years or older.

The study will have 2 phases: The Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 28 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights, and a minimum 14-day Follow-up Period before an End of Study (EOS) Visit.

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead electrocardiograms (ECGs), vital signs, weight, height, clinical hematology and chemistry analysis and urinalysis, and suicidality.

Screening Period

The Screening Period will begin no more than 28 days before the subject is randomized. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject complains of difficulties with sleep maintenance and/or early morning awakening. Screening assessments will include the ISI, as well as the Epworth Sleepiness Scale (ESS), STOPBang, International Restless Legs Scale (IRLS), and Munich Parasomnia Scale (MUPS), collectively called the Sleep Disorders Screening Battery (SDSB). Other assessments administered will include the FSS and EQ-5D-3L. Additional eligibility criteria will be assessed and safety assessments including the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be conducted.

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

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, and provided that the Sleep Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and

frequency of nights with symptoms of insomnia, subjects will undergo the second screening visit. (Subjects who are not eligible based on Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day -17 and Day -14. On this and all nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test.

After check-in has been completed, study personnel will familiarize subjects with the postural stability assessment (Cognitive Drug Research [CDR] posture assessment) and will also conduct a minimum of 2 training sessions for the cognitive performance assessment battery (PAB). 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.. Within 5 minutes of morning waketime, the CDR posture assessments and PAB assessments will be administered under the same conditions (eg, timing of assessments relative to waketime, ambient lighting), as will be employed during the testing sessions. The CDR posture and PAB assessments at this time are for familiarization purposes only. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG will be reviewed for exclusion criteria related to symptoms of sleep apnea and/or periodic limb movement disorder. Subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period.

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 subjects will take PBO each night immediately (ie, within 5 minutes) before bedtime (defined as the time the subject intends to try to fall asleep). They will be reminded that they must remain in bed for at least 7 hours each night and maintain a regular bedtime and waketime throughout the study, according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals and use of caffeine and alcohol.

When subjects have completed the Sleep Diary on at least 7 consecutive mornings after taking PBO on the preceding nights, the diary will be reviewed for continued eligibility with regard to whether the subject continues to report sWASO $\geq$60 minutes on at least 3 of the 7 nights, as well as the schedule and duration of time spent in bed. Subjects who are still eligible will return to the clinic for the first of 2 consecutive nights on which PSG will be recorded. The first of these 2 nights must be between Day -10 and Day -7. In the evening, before the PSG recording, the ISI, FSS, and EQ-5D-3L will be assessed. The ISI score will be reviewed for eligibility, and safety assessments will be conducted. Study personnel will administer study drug to subjects within 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second screening visit. Subjects will then undergo an 8-hour PSG. The next morning, subjects will undergo assessments including the CDR posture and PAB assessments and will complete the Sleep Diary. The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that is safe for them to do so.

Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects within 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will undergo postural stability and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic after the investigator determines that is safe for them to do so.

Subjects will continue to take study drug at home within 5 minutes before bedtime and they will continue to complete the Sleep Diary each morning within 1 hour after morning waketime. 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 Period

On Day 1, the Run-in Period will end and the Baseline Period will take place. Subjects will be admitted to the clinic and the ISI, FSS, and EQ-5D-3L will be administered. Blood and urine samples will be collected for routine safety assessments, an ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period.

Treatment Period

The Treatment Period will begin on Day 1 and will continue until Day 31. Eligible subjects will continue immediately to the Randomization Phase / Treatment Period. They will be randomized in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO.

Within 5 minutes before the subject's MHB, study drug will be administered and an 8-hour overnight PSG will be initiated. At completion of the PSG recording the following morning (Day 2), postural stability will be assessed and the PAB will be conducted immediately thereafter. Subjects will complete the Sleep Diary. They may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by an overnight PSG. The next morning (Day 3), CDR posture and PAB assessments will be conducted and a PK sample will be obtained. Subjects will complete the Sleep Diary. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may then leave the clinic after the investigator determines that is safe for them to do so. Study drug will be dispensed and subjects will be provided with instructions to continue completing the Sleep Diary each morning within 1 hour of waketime and taking study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period.

On Day 29, subjects will return to the clinic. Study drug will be administered within 5 minutes before the subject's MHB, followed immediately by a PSG. On the morning of Day 30, CDDR posture and PAB assessments will be conducted. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, CDR posture and PAB assessments will be conducted and a PK sample will be obtained. Then the ISI, FSS, EQ-5D-3L and PGI-Insomnia will be administered. Blood and urine samples will be collected for routine safety assessment. An ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Then, after the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic.

Follow-up Period

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

At least 14 days but no more than 18 days after completion of the Treatment Period subjects will return to the clinic for the EOS Visit. The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) and eC-SSRS will be administered, and routine safety assessments will be conducted.

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug, to complete an Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and the AE must be followed to resolution or for 2 weeks, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

Interim Analysis

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately 475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study.

This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter.

Cataplexy Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls) will be used to identify all cases; these will then be flagged for review by the Adjudication Committee. To assist in the preparation of narratives about such events and to support the Committee's adjudication process, investigators and site personnel will be instructed to query subjects who report any of the above events for supplemental information about the events, using a questionnaire provided for this purpose.

End of Study

Estimates for End of Study are as follows:

- The end of the study will be the date of the last study visit for the last subject in the study.
- The study will begin in approximately April 2016 and will end on or before June 2017.

The estimated duration for each subject on study is anticipated to be a maximum of 81 days (11.5 weeks) consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 28 days plus Treatment Period plus Follow-up Period and EOS Visit maximum of 53 days. A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study.

Number of Subjects

Approximately 2100 subjects will be screened to provide up to 950 randomized subjects. Subjects will be randomized to one of the following treatment arms: LEM5, LEM10, ZOL, or PBO, in an approximate 5:5:5:4 ratio (n=250:250:250:200). Randomization will be stratified by country and age group (55 to 64 years old; 65 years or older). At least 60% of the subjects will be age 65 years or older.

Inclusion Criteria

1. Male age 65 years or older or female age 55 years or older at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the subject is not eligible)
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of subjective WASO (sWASO) typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At Screening: Reports habitual bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. At Screening and at check-in before the first PSG during the Run-in Period: ISI score ≥15
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary on the 7 most recent mornings (minimum 5 of 7 for eligibility) before the second screening visit, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that neither bedtime, (defined as the time the subject attempts to try to sleep), nor waketime (defined as the time the subject gets out of bed for the day)

deviates more than 1 hour on more than 2 nights from the calculated MHB or median habitual waketime (MHW), respectively, from the screening Sleep Diary entries

9. 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 second screening visit, such that there is not more than 2 nights with time spent in bed duration < 7 hours or > 9 hours
10. During the Run-in Period: Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary on the 7 most recent mornings before the first PSG during the Run-in Period, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
11. During the Run-in Period: Reconfirmation of regular bedtimes and waketimes as defined in Inclusion Criterion 8
12. During the Run-in Period: Reconfirmation of sufficient duration of time in bed (TIB) as defined in Inclusion Criterion 9
13. During the Run-in Period: Objective (PSG) evidence of insomnia as follows:
    a) WASO average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes, AND
    b) SE average ≤ 85% on the 2 consecutive PSGs, with neither night >87.5%
14. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
15. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

Exclusion Criteria

1. A current diagnosis of sleep-related breathing disorder, 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:
    a. STOPBang score ≥5
       or Yes to ≥2 STOP questions and male
       or Yes to ≥2 STOP questions and body mass index (BMI) >35 kg/m^2
       or Yes to ≥2 STOP questions and neck circumference 17 inches / 43 cm in male or 16 inches / 41 cm in females
    b. International Restless Legs Scale score ≥16
    c. Epworth Sleepiness Scale score >7
2. Reports symptoms potentially related to narcolepsy on a screening questionnaire, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy
3. On the MUPS, (a) a history of symptoms of Rapid Eye Movement (REM) Behavior Disorder, sleep-related violent behavior, sleep-driving, or sleep-eating, or (b) symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study
4. Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second screening visit
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening
6. Beck Anxiety Index (BAI) score >15 at Screening
7. Habitually naps during the day more than 3 times per week
8. Is a female of childbearing potential

   Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, and are postmenopausal 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).

9. 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.
10. History of drug or alcohol dependency or abuse within approximately the previous 2 years
11. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than21 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
12. Known to be positive for human immunodeficiency virus
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
14. A prolonged QT/QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms)
15. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal, neurological or psychiatric disease or malignancy other than 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, including the ability to perform tasks on the cognitive PAB.
16. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
17. 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 assessment, including the ability to perform the PAB.
18. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the eC-SSRS administration during the Prerandomization Phase (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)
19. Any lifetime suicidal behavior (per the Suicidal Behavior section of the eC-SSRS)
20. Scheduled for surgery during the study
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week before the first dose of study medication (Run-in Period). (A list of prohibited concomitant medications is presented in Appendix 3 of the protocol)
22. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 2 weeks before Screening, or between Screening and Randomization (other than study medication during the Run-in Period)
23. Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study
25. A positive drug test at Screening, Run-In, or Baseline, or unwilling to refrain from use of recreational drugs during the study
26. Hypersensitivity to lemborexant or zolpidem or to their excipients
27. 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
28. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Test drug

Lemborexant 5 mg or 10 mg, or lemborexant-matched placebo taken orally in tablet form each night for 30 consecutive nights immediately before the time the subject intends to try to sleep

Comparator drug

Zolpidem tartrate extended release 6.25 mg or zolpidem-matched placebo taken orally in tablet form each night for 30 consecutive nights immediately before the time the subject intends to try to sleep

Run-in Period

All subjects will receive 1 lemborexant-matched placebo tablet and 1 zolpidem-matched PBO tablet in a single-blind manner during the Run-in Period

Treatment Period

During the Treatment Period, all subjects will receive 2 tablets as described below according to the treatment arm to which the subject has been randomized:

LEM5: 1 zolpidem-matched placebo tablet and 1 lemborexant 5 mg tablet

LEM10: 1 zolpidem-matched placebo tablet and 1 lemborexant 10 mg tablet

ZOL: 1 zolpidem 6.25 mg tablet and 1 lemborexant-matched placebo tablet

PBO: 1 zolpidem-matched placebo tablet and 1 lemborexant-matched placebo tablet

Duration of Treatment

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

Concomitant Drug/Therapy

Caffeine will be permitted in limited quantities during the study. Subjects will be advised to limit caffeine consumption to ≤4 cups of caffeinated beverages per day, or ≤400 mg caffeine per day. They will be instructed to avoid caffeine after 13:00 on days when they are scheduled for a PSG recording and after 18:00 on all other days during the study.

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcoholic drinks on any day during the study, but will be instructed not to consume any alcohol within 3 hours before bedtime. They must not consume any alcohol on days when they are scheduled for a PSG recording. Compliance with these restrictions will be monitored by specific questions on the Sleep Diary.

Prohibited medications include strong and moderate 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 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 Appendix 3 of the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

If a subject starts any prohibited medication or therapy 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.

Assessments

Screening Assessments (administered only at first screening visit)

Sleep Disorders Screening Battery

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

- ESS: a questionnaire that asks the subject to rate their probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, which assesses the severity of daytime sleepiness
- MUPS: a scale comprising 21 questions asking whether the subject has experienced phenomena related to the International Classification of Sleep Disorders Version 2 classified parasomnias (eg, enuresis, sleepwalking, sleep paralysis) along with a time frame for occurrence of these experiences ranging from within past month to lifetime and frequency within the time frame ranging from occasionally to almost every night.

Beck Depression Inventory – II

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

Beck Anxiety Inventory

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

Efficacy Assessments

Polysomnography (PSG)

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

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

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

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per TIB, calculated as TST/interval from lights off until lights on
- WASO: minutes of wake from the onset of persistent sleep until lights on
- WASO2H: minutes of wake during the interval from 240 minutes after lights off until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least one epoch of wake, after onset of persistent sleep, and including any terminal awakening)

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

- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening cannot be interrupted by stage N1, but must be interrupted by stage N2, N3, or REM
- Number of long awakenings

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

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

Electronic Sleep Diary

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the study. This Sleep Diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety. In addition, the Sleep Diary will include questions that relate to morning sleepiness and to alcohol consumption.

Sleep parameters:

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

Quality of Sleep:

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

Morning Sleepiness:

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

The morning sleepiness question that is part of the electronic Sleep Diary will also be asked verbatim, using a paper-and-pencil format, at 1.5 hours after waketime each morning the subject is in the clinic following a PSG recording. The rating on this question will be taken into consideration by the investigator when making the determination about whether it is safe for the subject to be discharged from the clinic.

Alcohol Consumption:

The Sleep Diary will include questions to determine both whether the subject consumed alcohol the previous day within 3 hours before bedtime, or exceeded the daily maximum of 2 alcoholic drinks, or both.

Insomnia Severity Index

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

Fatigue Severity Scale

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS score is the sum of all responses to the 9 questions. Higher scores indicate greater fatigue.

Pharmacokinetic Assessments

A single blood sample for plasma concentrations of lemborexant and its metabolites M4, M9 and M10 or zolpidem will be taken at predefined visits. The time and date of the 2 most recent doses before each sample will be documented in the electronic case report form (eCRF).

Pharmacodynamic Assessments

Postural stability using the CDR Posture Assessment

Postural stability will be assessed using an apparatus similar to the Wright ataxiameter, and referred to as the CDR posture device. The CDR posture device measures directional trunk movements (ie, body sway) through a cord placed around the subject's waist and connected to the ataxiameter. Subjects will stand on a firm surface with feet comfortably apart, either barefoot or wearing socks. The standing position and barefoot/socks conditions will be the same for a given subject at each postural stability assessment timepoint. They will be instructed to stand as still as possible with eyes closed for 1 minute. On the evening of the Screening PSG visit, subjects will be introduced to the CDR posture assessment. On the morning after the Screening PSG, subjects will complete a CDR posture assessment session for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, starting within 5 minutes of morning waketime, at bedside) as during the testing sessions at subsequent visits.

Body sway is detected through the cable around the subject's waist by the ataxiameter and these data are transmitted to a laptop. Body sway is measured in units of 1/3° of the angle of arc. For ease in reporting these will be called arbitrary units, with a higher number indicating more body sway (less postural stability).

Cognitive Performance Assessment Battery

A computerized PAB will be administered on a laptop computer after the postural stability test. All tasks require a Yes/No button-press response. While completing the PAB, subjects will be in bed and ambient lighting will be maintained at a level of 80 – 100 lux at the subject's eye level. On the evening of the Screening PSG visit, before bedtime, subjects will be introduced to the PAB tasks and will undergo a minimum of 2 training sessions. If subjects cannot adequately perform the tasks during the training sessions, they will be excluded from further participation. On the morning after the Screening PSG, subjects will complete a session of the cognitive PAB for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, lighting, subject in bed) as during the testing sessions at subsequent visits.

The PAB comprises 9 tasks including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Numerical Working Memory, Spatial Working Memory, Word Recognition, and Picture Recognition. The full PAB will take approximately 18 minutes to complete. Four composite domain factor scores are calculated by combining outcome variables from the various tests. The four domain factor scores are Power of Attention, Continuity of Attention, Quality of Memory, and Speed of Memory Retrieval.

- Power of Attention
  - A composite score from the speed scores of 3 tests of attention
  - Reflects the ability to focus attention and process information

- Continuity of Attention
  - A composite score created by combining the accuracy scores from the tests of attention
  - Reflects the ability to sustain attention (vigilance)

- Quality of Memory
  - A composite score created by combining the accuracy measures from the two tests of working memory and the four tests of episodic memory
  - Reflects the ability to store information in memory and subsequently retrieve it

- Speed of Memory Retrieval
  - A composite score created by combining the reaction time scores from the two working memory tests and the two episodic recognition tests
  - Reflects time taken to retrieve information held in both working and episodic memory

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, and at the EOS Visit.

Columbia - Suicidality Severity Rating Scale

Suicidality will be assessed using a self-rated electronic version of the C-SSRS (eC-SSRS). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire

An assessment of withdrawal symptoms will be made using the T-BWSQ completed at the EOS Visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes –moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's score. Scores above 20 will be considered clinically significant**.** Symptoms on the T-BWSQ will be analyzed and presented separately from AEs in the clinical study report.

Other Assessments

EQ-5D-3L

The EQ-5D-3L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility. The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

Patient Global Impression – Insomnia

The PGI-Insomnia is a self-report assessment asking about a subjects' perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a) helped/worsened sleep, (b) decreased/increased time to fall asleep, (c) increased/decreased total sleep time, and 1 item related to perceived appropriateness of study medication strength. The first 3 items are answered on a 3-point scale (1=positive medication effect, 2=neutral medication effect, 3=negative medication effect) and the last item on a different 3-point scale (medication: 1=too strong, 2=just right, 3=too weak).

Bioanalytical Methods

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

Statistical Methods

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

Study Endpoints

Primary Endpoint(s)

The primary endpoint is:

- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 compared to ZOL

Secondary Endpoint(s)

Key Secondary Endpoints:

- Change from baseline of mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL
- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL

Additional Secondary Endpoints:

- Change from baseline of mean LPS, SE, WASO, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to PBO
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO
- Proportion of responders after Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that
    - Objective sleep onset response is defined as LPS $\leq$ 20 minutes (provided mean baseline LPS was > 30 minutes)
    - Subjective sleep onset response is defined as sSOL $\leq$ 20 minutes (provided mean baseline sSOL was > 30 minutes)
    - Objective sleep maintenance response is defined as WASO $\leq$ 60 minutes (provided mean baseline WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
    - Subjective sleep maintenance response is defined as sWASO $\leq$ 60 minutes (provided mean WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
- Safety and tolerability of LEM
- Change from baseline of the score from items 4 to 7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

Exploratory Endpoints

The following endpoints will be explored for LEM5 and LEM10. Except for PK endpoints, comparisons to ZOL and PBO will be made.

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the

first 7 days and last 7 days of the Treatment Period

- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
  - Change from baseline of sSOL on each of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
  - Change from baseline of sWASO on each of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period
  - Proportion of subjects whose sSOL is longer than at baseline for each of the first 3 nights, or whose mean sSOL is longer than at baseline for first 7 nights or second 7 nights of the Follow-up Period
  - Proportion of subjects whose sWASO is higher than at baseline for each of the first 3 nights, or whose mean sWASO is higher than at baseline for the first 7 nights or second 7 nights of the Follow-up Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period
- Change from baseline of mean minutes and mean percentage (a) per TIB and (b) per TST of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline of mean of median REM latency, mean number of awakenings, and mean number of long awakenings on Days 1 and 2 and Days 29 and 30
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- Proportion of subjects who score ≥ 3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- PK of lemborexant and its metabolites M4, M9, and M10
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

Analysis Sets

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

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

The Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan (SAP).

The PK Analysis Set is the group of subjects who have at least one quantifiable plasma concentration of lemborexant or its metabolites, or zolpidem, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least one quantifiable lemborexant concentration data point as per the PK Analysis Set.

Efficacy Analyses

Definitions of Baseline

Baseline is defined as the means from the 2 PSGs during the Run-in Period for PSG-derived variables and the mean of the last 7 mornings before the first baseline PSG during the Run-in Period for Sleep Diary variables. For other endpoints, baseline data are captured during the Run-in Period and Baseline Period. Details will be specified in the SAP.

Control of Type I Error

A sequential gate-keeping procedure including the primary endpoint comparison (WASO2H of LEM10 vs ZOL) and the key secondary efficacy endpoint comparison (WASO2H of LEM5 vs ZOL) at Month 1 will control for type I error. In order to proceed from one step to the next the outcome must be significant at 0.05 (two-sided).

- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM5 compared to ZOL

This testing procedure controls the overall type I error rate of 0.05.

Analysis for the Primary Endpoint

Null Hypothesis: No difference exists in the mean change from baseline of the mean WASO2H of Days 29 and 30 for treatment with LEM10 as compared with ZOL.

Alternative Hypothesis: A difference exists in the mean change from baseline of the mean WASO2H of Days 29 and 30 for LEM10 compared to ZOL.

The WASO2H change from baseline (the mean of Days 1 and 2, and the mean of Days 29 and 30) will be analyzed using longitudinal data analysis (LDA) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), country, age group (55-64 years; 65 years or older), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The LDA model accounts for any missing data, and assumes that the missing data are missing at random. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. Provided that the data are normally distributed, least square (LS) means, difference in LS means of lemborexant dose compared to ZOL and PBO, 95% confidence intervals (CIs), and *P*-values will be presented. The primary comparison will be to compare the mean of Days 29 and 30 of LEM10 to ZOL; a key secondary comparison is to compare the mean of Days 29 and 30 of LEM5 to ZOL. Other pairwise comparisons will comparing Days 1 and 2 of LEM10 and LEM5 to ZOL, comparing Primary Endpoint

LEM10 and LEM5 to PBO at both time points are secondary.

Additional analyses will include investigating subgroup analyses and/or addition of covariates to the model of age, sex, race, BMI, country and/or other subgroups to be determined before unblinding.

Secondary Efficacy Analyses

Changes from baseline of mean units of body sway of the mean of Days 2 and 3 and the mean of Days 30 and 31 will be analyzed using the same LDA method as the primary endpoint. Where data are normally distributed, LS means, difference in LS means of LEM10 and LEM5 compared to ZOL and compared to PBO, 95% CIs and *P* -values will be presented for each time point. Corresponding to the key secondary objective, the key secondary comparisons will be to compare body sway on Days 2 and 3 of LEM10 and LEM5 to ZOL. The means of Days 30 and 31 comparing LEM5 and LEM10 to ZOL and PBO will be exploratory.

Using the same LDA method as for the primary endpoint, the secondary efficacy endpoints (change from baseline of the mean of the following endpoints: WASO2H of the mean of Days 1 and 2; WASO, LPS, SE, and TST of the mean of Days 1 and 2 and of the mean of Days 29 and 30; sSOL, sWASO, sSE, and sTST for the mean of the first 7 and last 7 days of the Treatment Period) will be analyzed. Corresponding to the secondary objectives, appropriate pair-wise treatment comparisons will be made. Where data are normally distributed, LS means, difference in LS means of each lemborexant dose compared to ZOL and compared to PBO, 95% CIs

and *P*-values at the appropriate time point will be presented.

The proportion of responders after the first 2 and last 2 nights of treatment based on PSG variables (WASO and LPS, respectively) will be analyzed using the Cochran-Mantel-Haenszel test, controlled for country and age group, for each dose of lemborexant compared to PBO and ZOL. The analysis will be similarly repeated for responder analysis based on Sleep Diary variables (sSOL and sWASO) over the first 7 and last 7 nights of treatment.

The change from baseline of the ISI total of four items on daytime functioning at Day 31 and the FSS score at Day 31 will be analyzed using analysis of covariance (ANCOVA), adjusted for the corresponding baseline value, age group, country, and treatment.

Exploratory and Pharmacodynamic Analyses

The change from baseline mean score of the quality of sleep item on the Sleep Diary for the means of the first 7 days and last 7 days of the Treatment Period will be analyzed using the same LDA method as the primary efficacy endpoints.

Changes from baseline in mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval for the PAB tasks will be analyzed similarly to the primary efficacy endpoints to compare each dose of lemborexant to ZOL and to PBO.

Rebound insomnia will be addressed by comparing Sleep Diary data (sSOL and sWASO) from each of the first 3 mornings, the first week, and the second week of the Follow-up Period with Sleep Diary data during the Screening Period. These data will be analyzed using ANCOVA, adjusted for country, age group and treatment. Rebound Insomnia will be defined as present if the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group. In addition, the proportion of subjects whose sSOL or sWASO on each of the first 3 nights and each of the 2 weeks of the Follow-up Period exceeds the subject's value on that parameter during the Screening Period will be summarized by treatment group.

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-up Period will be analyzed using the same LDA method as the primary efficacy endpoints.

The change from baseline of the mean of Days 1 and 2 and of the mean of Days 29 and 30 for the sleep architecture and other PSG endpoints (minutes and percentage [a] per TIB and [b] per TST of sleep stage N1, N2, N3, total NREM and REM; REM latency, DurLongAW, number of awakenings, number of long awakenings, REM episode frequency and duration, and mean REM/NREM cycle duration) will be analyzed as per the primary efficacy analyses.

Each item on the PGI-Insomnia at Day 31 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

The change from baseline in the EQ-5D-3L score at Day 31 will be analyzed using ANCOVA, adjusted for country, age group and treatment.

Pharmacokinetic Analysis

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

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK analysis data from this study will be pooled with relevant data from Phase 1 and 2 studies, and other Phase 3 studies if available. The effect of covariates (ie, demographics) on the PK of lemborexant will be evaluated. The PK model will be parameterized for apparent total clearance following extravascular administration (CL/F) and

volumes of distribution. Derived exposure parameters such as area under the concentration-time curve (AUC), maximum lemborexant plasma concentration (C_{max}) and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL/F and dosing history.

Pharmacodynamic Analysis

These analyses are described in the Secondary Efficacy Analyses, and Exploratory and Pharmacodynamic Analyses sections (above).

Pharmacokinetic/Pharmacodynamic Analysis

The PK/PD relationship between exposure to lemborexant and efficacy variables including but not limited to LPS and WASO, and safety variables including but not limited to morning sleepiness and frequently occurring treatment-emergent adverse events (TEAEs), will be explored graphically. Any emergent PK/PD relationships will be evaluated by population PK/PD modeling. The population PK/PD analysis plan will be described and results will be reported in a separate document.

Population PK and PK/PD analyses will be performed using NONMEM version 7.2 or later.

Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs and weight, suicidality (eC-SSRS), and T-BWSQ (including frequency and percentage of subjects with T-BWSQ score ≥3), along with change from baseline in laboratory safety test variables, ECGs, and vital sign and weight measurements, will be summarized by treatment group using descriptive statistics.

Other Analyses

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

Although ZOL is included in the study as an active comparator, comparison of ZOL to PBO, and comparison between LEM10 and LEM5 may be made to facilitate evaluation of study results.

Interim Analyses

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the conditional power will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved with the conduct of the study will have access to the interim data or the results of the interim analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis was concluded.

Sample Size Rationale

The sample size was estimated for the comparison of LEM10 with ZOL with respect to the mean change from baseline of WASO2H at Month 1, on the basis of a two-sided test at the 0.05 α-level.

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the SD of change from baseline for WASO2H is assumed to be 38 minutes. The LS mean treatment difference at Days 14/15 from Study 201 for WASO2H of LEM10 compared with PBO was -11 min. On the basis of the Food and Drug Administration (FDA) Center for Drug Evaluation Research Statistical Review of Ambien CR (zolpidem tartrate extended release/modified release) New Drug Application filing, ZOL may have approximately -1 to -2 minutes treatment effect on WASO2H compared to PBO if ZOL is dosed at bedtime. Therefore, assuming a treatment difference in WASO2H of -10 minutes, a sample size of 250 per treatment group at 5% (2-sided) level of significance has 84% power for comparing LEM10 with ZOL.

Power is also estimated for the key secondary objective, the comparison of LEM5 and LEM10 to ZOL on postural stability in the morning. For the assessment of postural stability using body sway, a 7-unit difference between active treatment and PBO with respect to change from time-matched baseline data is proposed to be clinically meaningful. A difference of 7 units represents a 35% change relative to placebo, which has been suggested to be a minimally clinically meaningful increase in body sway that is associated with a blood alcohol level of 0.5 g/L and an increased risk of falling. Assuming a treatment difference of 3.5 units and SD=12, a sample size of 250 per treatment group at 5% (2-sided) level of significance has 90% power for detecting a statistically significant difference between LEM and ZOL.

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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
CFR	Code of Federal Regulations
CI	confidence interval
CL	total clearance
CL/F	apparent total clearance following extravascular administration
C_{max}	maximum observed concentration
CPMP	Committee for Proprietary Medicinal Products,
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
DORA	dual orexin receptor antagonist
EASS	events associated with special situations
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EEG	electroencephalogram
EMG	electromyography
EOS	end of study
ESS	Epworth Sleepiness Scale
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale

Abbreviation	Term
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IR	immediate release
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
IxRS	an interactive voice and web response system
KSS	Karolinska Sleepiness Scale
LDA	longitudinal data analysis
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
MHB	median habitual sleep time
M-MSLT	modified multiple sleep onset latency test
MUPS	Munich Parasomnia Scale
NREM	non-REM sleep
PAB	performance assessment battery
PBO	placebo
PD	pharmacodynamic(s)
PGI	Patient Global Impression
PI	principal investigator
PK	pharmacokinetic(s)
PSG	polysomnography
PT	preferred term
QTcF	QT interval corrected for heart rate by Fridericia's formula
RBC	red blood cells
REM	rapid eye movement (sleep stage)
SAE	serious adverse event
SAP	statistical analysis plan
SDSB	Sleep Disorders Screening Battery

Abbreviation	Term
SE	sleep efficiency
SOC	system organ class
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTIB	subjective time in bed
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
T-BWSQ	Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
TEAE	treatment-emergent adverse event
TIB	time in bed
TST	total sleep time
US	United States
WASO	wake after sleep onset
WASO2H	wake after sleep onset in the second half of the night
WBC	white blood cells
ZOL	zolpidem tartrate extended release 6.25 mg (Ambien CR®)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- 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. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. 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 90 investigational sites in North America and Europe.

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 provided to each site.

7 INTRODUCTION

7.1 Indication

7.1.1 Current Therapeutic Options

Insomnia is a sleep disorder characterized by difficulties with sleep onset, sleep maintenance, or early morning awakening, in association with a complaint of impairment during the daytime. Insomnia is a widespread problem in industrialized nations, with approximately 30% of the population having symptoms and at least 6% meeting diagnostic criteria for insomnia meriting treatment. Currently available pharmacological treatments used for insomnia include benzodiazepines, non-benzodiazepine γ-aminobutyric acid (GABA) receptor agonists (GABAergics), a recently approved dual orexin receptor antagonist (DORA), sedating antidepressants, melatonin and melatonin agonists, antihistamines, and other prescription and non-prescription medications with sedative properties.

The current commercial environment is generic, with the non-benzodiazepine, zolpidem (Ambien®), leading in prescriptions in the US. Other so-called "z-drugs" including zaleplon and eszopiclone, contribute substantially to market share as well. However, there are efficacy and safety concerns associated with the use of z-drugs, particularly zolpidem, particularly in older patients. This limited efficacy is characteristic of short-acting non-benzodiazepine hypnotics and represents an important unmet medical need, as sleep maintenance insomnia is the most prevalent type of insomnia experienced in aging. Up to 50% of individuals over age 55 report difficulty maintaining sleep. The recently approved DORA, suvorexant, was shown in clinical trials to significantly improve sleep maintenance insomnia, but at the starting dose approved for use, showed suboptimal efficacy.

7.1.2 Lemborexant (E2006)

7.1.2.1 Mechanism of Action

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

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

7.1.2.2 Clinical Experience with Lemborexant

7.1.2.2.1 PHASE 1

E2006-A001-001 (Study 001): single ascending dose study. This study included healthy subjects and otherwise healthy subjects with primary insomnia. In addition to determining

the safety and tolerability of single doses, the study provided preliminary evidence of efficacy in the target patient population.

E2006-A001-002 (Study 002): multiple ascending dose study. This study enrolled healthy adult and elderly subjects, each of whom was dosed with lemborexant or placebo 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 CYP3A lead to higher plasma concentrations of lemborexant; and (2) strong inducers of CYP3A lead to notably lower plasma concentrations of lemborexant. The study also demonstrated a weak effect of lemborexant on CYP2B6 activity and no effect on CYP3A activity.

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

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

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

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

in average time to sleep onset in the morning hours, supporting the safety of these doses and their use in Phase 3 studies.

7.1.2.2.2 PHASE 2

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

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

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

Overall, data from the clinical program to date have shown an acceptable safety and tolerability profile of lemborexant, and efficacy on both objective and subjective measures of sleep onset and sleep maintenance.

7.2 Study Rationale

The purpose of this study is to provide important information to begin to improve on the current treatment paradigm for older patients with sleep maintenance insomnia. Zolpidem has been shown to improve sleep onset insomnia. The immediate release (IR) formulation of zolpidem is not, however, indicated for sleep-maintenance insomnia. The extended release formulation, zolpidem tartrate extended release 6.25 mg (Ambien CR®), was approved by the Food and Drug Administration (FDA) for the treatment of sleep maintenance symptoms as well as for sleep onset difficulties. However, 2 studies, one using 12.5 mg in adults and the other studying 6.25 mg in elderly patients, reported that effects on WASO after nights 1 and 2 of treatment were only statistically significantly different from placebo for the first 6 hours (adults) or first 5 hours (elderly) of the 8-hour sleep period. After 2 weeks of treatment, WASO was significantly decreased for only the first 5 hours (adults) and first 4 hours (elderly) of the 8-hour sleep period. Given that this is the time of night when most sleep

maintenance difficulties are experienced, particularly by elderly individuals, there is an unmet need that has not been effectively addressed with zolpidem tartrate extended release 6.25 mg (Ambien CR®, ZOL). In brief, while ZOL improves sleep maintenance more than the IR formulation, it does not sufficiently decrease WASO in the second half of the night (WASO2H). Nonetheless, ZOL was approved based on data for the first 6 hours of the sleep period. It should be noted that the pivotal studies for ZOL were based on data from 3-week trials analyzed for Nights 1/2 and 15/16. A comparison of lemborexant with ZOL, especially with respect to sleep maintenance, would provide clinically meaningful information for clinicians and patients.

8 STUDY OBJECTIVES

8.1 Primary Objective

Demonstrate using PSG that 10 mg lemborexant (LEM10) is superior to zolpidem tartrate extended release 6.25 mg (Ambien CR; ZOL) on objective sleep maintenance as assessed by wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

8.2 Secondary Objectives

8.2.1 Key Secondary Objectives

1. Demonstrate that 5 mg lemborexant (LEM5) is superior to ZOL on objective sleep maintenance as assessed by WASO2H after the last 2 nights of treatment

2. Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment

8.2.2 Additional Secondary Objectives

3. Compare the efficacy of LEM5 and LEM10 to ZOL on other PSG variables (LPS, SE, WASO, and total sleep time [TST]) after the first 2 nights and the last 2 nights of treatment and on Sleep Diary variables (subjective sleep onset latency [sSOL], subjective SE [sSE], subjective WASO [sWASO], and subjective TST [sTST]) over the first 7 nights and last 7 nights of treatment.

4. Confirm the efficacy of LEM5 and LEM10 compared to PBO on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment

5. Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary sSOL and sWASO

6. Evaluate the safety and tolerability of lemborexant

7. Compare the efficacy of LEM5 and LEM10 to ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) at the end of treatment

8. Compare the safety of LEM5 and LEM10 to ZOL and PBO on cognitive performance in the morning after the first 2 nights of treatment

8.2.3 Exploratory Objectives

1. Explore the effects of LEM5, LEM10, ZOL and PBO on:

a) Subjective quality of sleep

b) Postural stability in the morning after the last 2 nights of treatment

c) Cognitive performance after the last 2 nights of treatment

d) Rebound insomnia in the 2 weeks following 30 days of treatment

e) Subjective ratings of morning sleepiness during and following completion of treatment

f) Sleep architecture parameters and other PSG variables

g) Health outcomes on the Patient Global Impression - Insomnia (Patient Global Impression [PGI]-Insomnia) and EQ-5D-3L

h) Withdrawal symptoms after completion of treatment

2. Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10

3. Conduct population PK modeling for lemborexant

4. Explore PK/PD relationships between lemborexant concentrations and efficacy and safety variables

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ie, ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males 65 years or older or females 55 years or older. At least 60% of the population will be age 65 years or older.

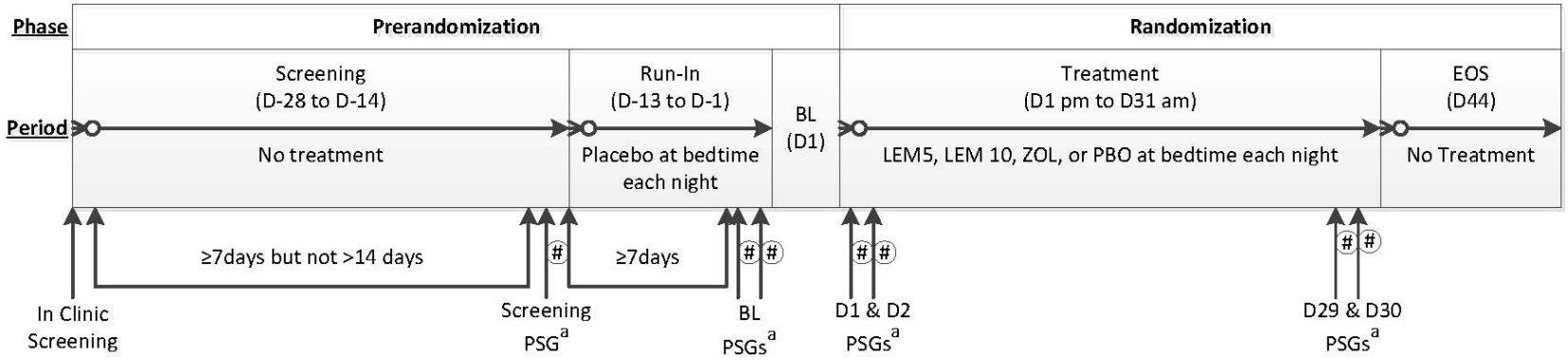
The study will have 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 28 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights followed by a minimum 14-day interval before an End of Study (EOS) Visit.

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding AEs, 12-lead electrocardiograms (ECGs), vital signs, weight, height, clinical hematology and chemistry analysis and urinalysis, and suicidality.

Estimates for End of study are as follows:

- The end of the study will be the date of the last study visit for the last subject in the study.
- The study will begin in approximately Apr 2016 and will end on or before Jul 2017.
- The estimated duration for each subject on study is anticipated to be a maximum of 81 days / 11.5 weeks (Screening Period plus Run-in Period plus Baseline Period maximum of 28 days plus Treatment Period plus Follow-up Period and EOS Visit maximum of 53 days). A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study.

The study design is shown in Figure 1.



= CDS Posture and cognitive PAB assessments in the morning following the PSG assessment.
a: All PSG visits will require an overnight stay in the clinic. At least 5 nights must intervene between the second BL PSG and BL (D1).

Figure 1 Schematic Diagram of Study Design

"D" refers to the study day.

BL = baseline, EOS = End of Study, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PAB = performance assessment battery, PBO = placebo, PSG = polysomnography, ZOL = zolpidem tartrate extended release 6.25 mg.

9.1.1 Prerandomization Phase

9.1.1.1 Screening Period

The Screening Period will begin no more than 28 days before the subject is randomized. At the first screening visit (Visit 1), informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject complains of difficulties with sleep maintenance or early morning awakening, or both. Screening assessments will include the ISI, as well as the Epworth Sleepiness Scale (ESS), the STOPBang, the International Restless Legs Scale (IRLS), and the Munich Parasomnia Scale (MUPS), collectively called the Sleep Disorders Screening Battery (SDSB). Additional eligibility criteria will be assessed and safety assessments will be conducted as described in Section 9.5.1.2 and summarized in Table 4.

jects will be provided with an electronic device on which they will complete the Sleep Diary and will be trained in the use of this device. Site staff will instruct subjects to complete the diary each morning within 1 hour after morning waketime and will emphasize the importance of doing so. The Sleep Diary entries will be reviewed by site staff at least weekly throughout the study to ensure subject compliance with completion of the Sleep Diary and to ensure that study restrictions are met pertaining to duration of time spent in bed, , and use of alcohol.

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, and provided that the Sleep Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the second screening visit. (Subjects who are not eligible on the basis of Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day -17 and Day -14. On this and all nights on which PSG is to be recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test.

After check-in has been completed, study personnel will familiarize subjects with the postural stability assessment (CDR posture assessment) and will also conduct a minimum of 2 training sessions for the cognitive performance assessment battery (PAB). 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. Within 5 minutes of morning waketime, the CDR posture and PAB assessments will be administered under the same conditions (eg, timing of assessments relative to waketime, ambient lighting), as will be employed during the testing sessions. The CDR posture and PAB assessments at this time are for familiarization purposes only. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG will be reviewed for exclusion criteria related to absence of symptoms of sleep apnea and/or periodic limb

movement disorder, subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period.

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, subjects will take PBO each night immediately (ie, within 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 throughout the study according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals and use of caffeine and alcohol.

When subjects have completed the Sleep Diary on at least 7 consecutive mornings after taking PBO on the preceding nights, the diary will be reviewed for continued eligibility with regard to whether the subject continues to report sWASO ≥60 minutes on at least 3 of the 7 nights, as well as the schedule and duration of time spent in bed. Subjects who are still eligible will return to the clinic for the first of two consecutive nights on which PSG will be recorded. (Subjects who are not eligible on the basis of Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) The first of these 2 nights must be between Day -10 and Day -7. In the evening before the PSG recording, the ISI, the FSS, and the EQ-5D-3L will be assessed. The ISI score will be reviewed for eligibility and safety assessments will be conducted. Study personnel will administer study drug to subjects within 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second screening visit. Subjects will then undergo an 8-hour PSG. The next morning, subjects will undergo assessments including the CDR posture and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that is safe for them to do so.

Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects within 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will undergo postural stability and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic only after the investigator determines that is safe for them to do so.

Subjects will continue to take study drug at home within 5 minutes before bedtime and they will continue to complete the Sleep Diary each morning within 1 hour after morning waketime. 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 take place. Subjects will be admitted to the clinic and the ISI, FSS, and EQ-5D-3L will be administered. Blood and urine samples will be collected for routine safety assessments, ECG will be performed, and vital signs and weight will be assessed. The electronic Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized and will begin the Treatment Period.

9.1.2 Randomization Phase

9.1.2.1 Treatment Period

The Treatment Period will begin on Day 1, and will continue until Day 31. Eligible subjects will continue immediately to the Randomization Phase / Treatment Period. They will be randomized in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO.

Within 5 minutes before the subject's MHB, study drug will be administered and an overnight PSG will be initiated. At completion of the PSG recording the following morning (Day 2), postural stability will be assessed and the PAB will be conducted immediately thereafter. Subjects will complete the Sleep Diary. They may then leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by an overnight PSG. The next morning (Day 3), the CDR posture and PAB assessments will be conducted and a PK blood sample will be obtained.

Subjects will complete the Sleep Diary. The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may then leave the clinic after the investigator determines that is safe for them to do so. Study drug will be dispensed, and subjects will be provided with instructions to continue to complete the Sleep Diary each morning within 1 hour of waketime and to take study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period.

On Day 29, subjects will return to the clinic. Study drug will be administered within 5 minutes before the subject's MHB, followed immediately by a PSG. On the morning of Day 30, postural stability will be assessed and the PAB will be conducted. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, postural stability and PAB assessments will be conducted and a PK sample will be obtained. Then the ISI, FSS, EQ-5D-3L and PGI-Insomnia will be administered. Blood and urine samples will be collected

for routine safety assessment. An ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Then, 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

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

At least 14 days but no more than 18 days after completion of the Treatment Period, subjects will return to the clinic for the EOS Visit. The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) and eC-SSRS will be administered, and routine safety assessments will be conducted.

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug, to complete an Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and the AE must be followed to resolution or for 2 weeks, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Randomization

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

9.2.2 Run-In

Insomnia trials are associated with large placebo effects. This study will include a placebo Run-in Period to exclude subjects who show a response to placebo or who lack sufficient WASO2H at baseline to show an active treatment response.

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

9.2.3 Efficacy Assessments

This study focuses on WASO2H, a measure of sleep maintenance in the second half of the night, as the primary endpoint. The rationale for the selection of this endpoint is based on the loss of effect of ZOL on sleep maintenance at the end of the sleep period. However, any benefit on WASO2H observed with lemborexant must not be due to a worsening of sleep latency or continuity at the beginning of the night. Therefore, analyses of both LPS and total WASO as well as other PSG variables (eg, TST, number and duration of awakenings) will be conducted to confirm the efficacy of lemborexant on sleep onset and sleep maintenance.

9.2.4 Morning Residual Effects on Postural Stability and Cognitive Performance

Non-benzodiazepine sleep-inducing agents such as zolpidem have been associated with motor and cognitive impairment, and laboratory studies have evaluated these impairments both during the middle of the night several hours postdose, and in the morning hours shortly after awakening. Of clinical importance is that the elderly are particularly sensitive to effects of zolpidem on postural stability, which is especially problematic given the increased risk of falls in the elderly.

Moderate to large treatment effects versus placebo on measures of postural stability and cognitive performance have been reported for both 5 mg and 10 mg doses of the IR formulation of zolpidem (Allain, et al., 2003), Mets, et al., 2010, and Boyle, et al., 2009; reviewed in Stranks and Crowe, 2014). Larger impairments are observed near the C_{max} of the zolpidem IR formulation at approximately 1.5 hours postdose than at later timepoints relative to dosing, but there remains a moderate impairing effect of zolpidem even the next morning on certain cognitive domains including attention and memory (Stranks and Crowe, 2014).

With regard to postural stability as measured in this study, zolpidem is assumed to have the same effect on body sway as alcohol at 4.5 hours after dosing (Wesnes, et al., 2000). Further, there is consistent evidence that the effects on postural stability of hypnotic drugs are larger after the first one or two nights of dosing and dissipate thereafter, which has been explained as due to behavioral tolerance (Mets, et al., 2010). For this reason, the key secondary objective for the current study is to compare the effects of lemborexant to those of zolpidem on postural stability at the beginning of treatment, in the morning shortly after waketime on Day 2 and Day 3. Whether there are differential effects of lemborexant and zolpidem on postural stability at the end of treatment (Day 30 and Day 31) will be explored. Effects on cognitive performance in the morning shortly after waketime will be exploratory for both the beginning and end of treatment.

9.2.5 Cataplexy Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls) will be used to identify all cases; these will then be flagged for review by the Adjudication Committee. To assist in the preparation of

narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information about events of cataplexy or potential cataplexy events, using a questionnaire provided for this purpose.

9.2.6 Study Duration

The registration trials for zolpidem were 3 weeks in duration, with analyses of PSG efficacy data conducted after the first 2 doses and at the end of 2 weeks of active treatment. As noted, treatment benefit of zolpidem declined over time such that WASO2H, particularly in the last 2 hours of the night, was not different from placebo on Nights 15/16 in the zolpidem registration trials. In contrast, when lemborexant was studied for 15 nights of treatment in Study 201, the treatment benefit was maintained such that there was no significant difference in LPS, WASO, or WASO2H between the first 2 and last 2 nights of treatment. Study 304 includes 30 days of active treatment. Based on the results of Study 201, it is expected that there will not be a loss of efficacy of lemborexant between 2 weeks and 4 weeks of treatment.

Moreover, as the beneficial effects of zolpidem on WASO2H did not persist for 2 weeks, it is not expected that there will be statistically or clinically significant effects of ZOL at the end of the 30 days of treatment.

9.2.7 Age Group

When Study 201 data were analyzed separately for those aged 55 years and older, the apparent treatment effect of lemborexant versus placebo on WASO2H, as well as on WASO, was larger than for the full sample (all ages studied), suggesting that this group may be most likely to benefit from treatment. Table 1 shows the least square (LS) mean treatment difference between lemborexant and PBO for various dose groups and dose group combinations from Study 201 for the full sample and for those aged 55 and older. Caution must be exercised concerning the predictive ability of these data, however, since the observed variability in WASO2H was larger in the older subjects. For this reason, a conservative estimate of the expected treatment difference between lemborexant and PBO for WASO2H at the end of treatment was used for power analyses and sample size justification. Enrollment in this study is exclusively older subjects, aged 55 years and older. While the lower age is not the typical 65 years defining "elderly," it is physiologically meaningful, as insomnia incidence increases at middle age in both men and women, with a particularly steep increase in incidence in women at menopause. In addition, the homeostatic and circadian regulation of sleep are disturbed in many older individuals, which manifests most frequently as sleep maintenance insomnia in the second half of the night, and early morning awakening. The preponderance of sleep maintenance issues in the second half of the sleep period is clear from the literature as well as supported by analyses of data by age group from Study 201.

Table 1 Treatment Effect for Lemborexant versus Placebo (Study 201)

	Treatment Effect in Minutes (95% CI)		
	5 mg	**10 mg**	**5 and 10 mg combined**
Entire Subject Sample	-7.97 (-19.2, 3.23)	-11.8 (-23.6, -0.05)	-10.0 (-20.6, 0.55)
Aged 55 and Older	-23.9 (-43.8, -3.95)	-14.8 (-36.9, 7.36)	-20.2 (-40.1, -0.35)

CI = confidence interval

9.2.8 Time of Dosing

The time of dosing of study drug will be within 5 minutes before bedtime on nights in the clinic. On nights at home, subjects will be instructed to take study drug just before they intend to try to fall asleep, but as consistently as possible with respect to the time across the study.

9.2.9 Interim Analysis

An interim analysis is planned to be conducted after 50% of the subjects (approximately 475 subjects) have been randomized and have either completed Day 31 assessments or discontinued from the study. The purpose of this analysis is to determine the conditional probability that a statistically significant difference between LEM10 and ZOL on WASO2H will emerge at the end of treatment. This interim analysis will be conducted by an independent statistician external to the Sponsor. The role of the independent statistician and procedures undertaken to preclude potential bias will be detailed in the statistical analysis plan (SAP) and in the Charter.

9.3 Selection of Study Population

Approximately 2100 subjects will be screened and approximately 950 subjects will be randomized at approximately 90 sites in North America and Europe. 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

1. Male age 65 years or older or female, age 55 years or older at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder, as follows:

- Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the subject is not eligible)
- Frequency of complaint ≥ 3 times per week
- Duration of complaint ≥ 3 months
- Associated with complaint of daytime impairment

3. At Screening: History of subjective WASO (sWASO) typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At Screening: Reports habitual bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. At Screening and at check-in before the first PSG during the Run-in Period: ISI score ≥15
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary on the 7 most recent mornings (minimum 5 of 7 for eligibility) before the second screening visit, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that neither bedtime, (defined as the time the subject attempts to try to sleep), nor waketime (defined as the time the subject gets out of bed for the day) deviates more than 1 hour on more than 2 nights from the calculated MHB or median habitual waketime, respectively, from the Screening Sleep Diary entries
9. Confirmation of sufficient duration of TIB, as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that there is not more than 2 nights with TIB duration < 7 hours or > 9 hours
10. During the Run-in Period: Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary on the 7 most recent mornings before the first PSG during the Run-in Period, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
11. During the Run-in Period: Reconfirmation of regular bedtimes and waketimes as defined in Inclusion Criterion 8
12. During the Run-in Period: Reconfirmation of sufficient duration of TIB as defined in Inclusion Criterion 9
13. During the Run-in Period: Objective (PSG) evidence of insomnia as follows:

    a) WASO average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes AND

    b) SE average ≤ 85% on the 2 consecutive PSGs, with neither night >87.5%

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

9.3.2 Exclusion Criteria

1. A current diagnosis of sleep-related breathing disorder, 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:
   a. STOPBang score ≥5

      or Yes to ≥2 STOP questions and male

      or Yes to ≥2 STOP questions and body mass index (BMI) >35 kg/m^2

      or Yes to ≥2 STOP questions and neck circumference 17 inches / 43 cm in male or 16 inches / 41 cm in females

   b. International Restless Legs Scale score ≥16

   c. Epworth Sleepiness Scale score >7
2. Reports symptoms potentially related to narcolepsy on a screening questionnaire, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy
3. On the MUPS, (a) a history of symptoms of Rapid Eye Movement (REM) Behavior Disorder, sleep-related violent behavior, sleep-driving, or sleep-eating, or (b) symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study
4. Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index > 15 as measured on the PSG at the second screening visit
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening
6. Beck Anxiety Inventory (BAI) score >15 at Screening
7. Habitually naps during the day more than 3 times per week
8. Is a female of childbearing potential

   Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, are in the appropriate age group, and are postmenopausal 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).
9. 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

10. History of drug or alcohol dependency or abuse within approximately the previous 2 years
11. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or habitually consumes alcohol within the 3 hours before bedtime and 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
12. Known to be positive for human immunodeficiency virus
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
14. A prolonged QT/QTcF interval (QTcF > 450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms)
15. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal, neurological psychiatric disease or malignancy other than 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, including the ability to perform tasks on the cognitive PAB
16. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
17. 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, including the ability to perform the PAB
18. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the eC-SSRS administration during the Prerandomization Phase (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)
19. Any lifetime suicidal behavior (per the Suicidal Behavior section of the eC-SSRS)
20. Scheduled for surgery during the study
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week before the first dose of study medication (Run-in Period). (A list of prohibited concomitant medications is presented in Appendix 3)
22. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 2 weeks before Screening, or between Screening and Randomization (other than study medication during the Run-in Period)
23. Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study

25. A positive drug test at Screening, Run-In, or Baseline, or unwilling to refrain from use of recreational drugs during the study
26. Hypersensitivity to the study drugs (lemborexant or zolpidem) or to their excipients
27. 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
28. 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 ET Visit as soon as possible. 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 Treatment(s)

9.4.1 Treatment(s) Administered

Test drug

Lemborexant 5 mg, lemborexant 10 mg or lemborexant-matched placebo will be taken orally in tablet form at home each night for 30 consecutive nights, immediately before the time the subject intends to try to sleep.

Comparator drug

Zolpidem tartrate extended release 6.25 mg (Ambien CR) or zolpidem-matched placebo will be taken orally in tablet form at home each night for 30 consecutive nights, immediately before the time the subject intends to try to sleep.

Run-in Period

All subjects will receive 1 lemborexant-matched placebo tablet and 1 zolpidem-matched placebo tablet in a single-blind manner during the Run-in Period.

Treatment Period

During the Treatment Period, all subjects will receive 2 tablets as described below according to the treatment arm to which the subject has been randomized:

LEM5: 1 zolpidem-matched placebo tablet and 1 lemborexant 5 mg tablet

LEM10: 1 zolpidem-matched placebo tablet and 1 lemborexant 10 mg tablet

ZOL: 1 zolpidem 6.25 mg tablet and 1 lemborexant-matched placebo tablet

PBO: 1 zolpidem-matched placebo tablet and 1 lemborexant-matched placebo tablet

9.4.2 Identity of Investigational Product(s)

The sponsor will provide lemborexant tablets in strengths of 5 mg, 10 mg and lemborexant-matched placebo, identical in appearance. The comparator, zolpidem, will be obtained from commercial sources as zolpidem tartrate extended release 6.25 mg (Ambien CR 6.25) tablets, and the sponsor will provide placebo tablets identical in appearance to the zolpidem tablets. Tablets will be packaged in child-resistant 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 3. The subject will take 2 tablets a day; a single lemborexant or lemborexant-matched placebo tablet and a single zolpidem or zolpidem-matched placebo tablet. The placebo run-in card will contain a 17-day supply of lemborexant-matched placebo and zolpidem-matched placebo tablets per day. Each card for the Treatment Period will contain a 35-day supply of tablets of either lemborexant or lemborexant-matched placebo and either zolpidem or zolpidem-matched placebo depending on the dose, in double-blind, double-dummy 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

Zolpidem tartrate extended release 6.25 mg (Ambien CR 6.25)

Placebos to match lemborexant or zolpidem tartrate extended release 6.25 mg

9.4.2.3 Labeling for Study Drug

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

The following information has to be provided:

- For clinical trial use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

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

9.4.3 Method of Assigning Subjects to Treatment Groups

At Baseline, subjects will be randomized, in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO in a 5:5:5:4 ratio. Randomization will be stratified by country and by age group (55 to 64 years; 65 years or older). Randomization to study treatments will be based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

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

9.4.4 Selection of Doses in the Study

In Study 201, all doses studied met the first primary objective of balancing significant efficacy as measured by change from baseline in SE with sufficient safety measured by subjective sleepiness reported on the KSS. The second primary objective was also achieved, as there were no significant increases in the KSS at 1 hour after waketime at the end of treatment. However, there were dose-related increases in the KSS at both the beginning and end of treatment, and the rate of AEs of somnolence also increased with increasing dose level.

In Study 201, lemborexant 5 mg and 10 mg showed significant efficacy measured by SE, as well as decreases in sleep onset latency. These effects were maintained across the 15-day

Treatment Period. For sleep maintenance, lemborexant 10 mg showed significant decreases, and while the magnitude of decreases in WASO was less for 5 mg, there was a significant proportion of subjects whose WASO decreased substantially, providing evidence for clinical benefit of 5 mg on sleep maintenance as well.

Because of the observed dose-related increases in subjective sleepiness and AEs of somnolence in Study 201, Study 107 was conducted to obtain additional information about the risk of clinically meaningful morning residual sleepiness. The study assessed average sleep onset latency on the M-MSLT after a single dose of LEM5 or LEM10 versus PBO. The results indicated that the pre-specified threshold for a clinically meaningful decrease in average sleep onset latency was not met by either the 5 mg or 10 mg dose level of lemborexant, supporting their use in the Phase 3 clinical trials. Taken together with the efficacy and safety results for lemborexant 5 mg and 10 mg in the Phase 2 study, these dose levels were selected for the current study.

Regarding ZOL, the FDA-approved doses of Ambien CR are 6.25 mg (recommended dose for women and elderly patients) and 12.5 mg (highest recommended dose for non-elderly patients). In the present study, only the 6.25 mg dose of ZOL will be administered. Of note is that a maximum of 40% of the study sample will be in the age range of 55 to 64 years old, and stratification by age will be implemented to ensure that at least 60% will be 65 years or older. All of the subjects in the 55 to 64 years age group will be females.

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 immediately before the subject intends to sleep. When the subject is to sleep in the clinic for PSG, study personnel will administer study drug. On other nights, the subject will take study drug at home on as consistently a time schedule 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.

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

the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

Disclosure of information from the interim analysis (Section 9.7.3) will be limited as detailed in the Interim Analysis charter. No individuals involved with the conduct of the study will have access to this information.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Drug-Drug Interactions

Not applicable

9.4.7.2 Prohibited Concomitant Therapies and Drugs

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 alcoholic drinks on any day during the study, and will be advised not to consume any alcohol within 3 hours before bedtime. They must not consume alcohol on any days when they are scheduled for a PSG recording. Compliance with these restrictions will be monitored via questions on the Sleep Diary. If subjects cannot comply after an infraction and counseling, they may be discharged from the study.

Prohibited medications include strong and moderate 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 above) 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).

Non-pharmacological treatments such as cognitive behavioral therapy are also prohibited before screening and cannot be initiated at any time during the study.

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.

Any medication (including over-the-counter medications) or therapy administered to the subject within the last 3 months before Screening (ie, Prior Medications) or during the study, starting on the date of informed consent, will be recorded on the Prior and Concomitant Medication 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.

9.4.8 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 within 5 minutes before bedtime, and they will be reminded that their bedtime should be the same throughout the study. Subjects will be told that following these instructions about taking study medication is important for the treatment to be effective. Compliance will be monitored closely and determined at specific visits by tablet count. Tablets will be counted separately for tablets that are matched to lemborexant and tablets that are matched to zolpidem.

When subjects arrive for the first screening/baseline PSG during the Run-in Period, and the treatment compliance check indicates that a subject has missed any doses, the subject will be counseled by site personnel. If the subject has missed more than 1 dose, and given that the subject continues to meet eligibility criteria, the investigator must consult with the sponsor prior to the subject being randomized and come to a collaborative decision on whether the subject should continue in the study. When subjects arrive for Baseline, and the treatment compliance check indicates that a subject has missed any doses, the investigator must use clinical judgment to decide if the subject should continue in the study.

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

9.4.9 Drug Supplies and Accountability

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

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

- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572
- A signed and dated curriculum vita of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vita
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

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

The study drugs/ and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA; Medicine and Healthcare products Regulatory Agency. As applicable, all unused study drugs/ and empty and partially empty containers from used study drugs/ are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) 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. In some regions, study drugs/ may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

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

Study sites are also responsible for tracking receipt, distribution, and return of all study equipment (eg, Sleep Diary devices) to the sponsor or designated entity.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity (where allowed). To secure protected health information, only actual year of birth will be collected, and the following convention for month and day of each subject's date of birth will apply to all subjects in all countries.: If on the date of the initial screening visit a subject has had a birthday in the current calendar year, the month and day of the subject's date of birth will be documented as January 1. Otherwise, the month and day of the subject's date of birth will be documented as December 31.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Sleep, medical, and psychiatric history and current medical conditions will be recorded at the Screening Visit. All sleep, medical, and psychiatric history within 5 years must be noted in the Medical History and Current Medical Conditions eCRF.

Physical examinations (full or brief) will be performed as described in Section 9.5.1.5.7.

9.5.1.2.2 Sleep Disorders History and Screening Battery

The SDSB will be administered only at the Screening Visit, and will include the:

- StopBANG: a list of eight questions to be answered Yes or No, which screens potential subjects for obstructive sleep apnea (Chung et al., 2008)
- IRLS: a subjective scale comprising ten questions, which measures disease of symptoms of restless legs syndrome (Abetz et al., 2006)
- ESS: a questionnaire that asks subjects to rate their probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most

people engage in during their daily lives, which assesses the severity of daytime sleepiness (Johns, 1992)

- MUPS: a scale comprising 21 questions asking whether the subject has experienced phenomena related to International Classification of Sleep Disorders Version 2 classified parasomnias (eg, enuresis, sleepwalking, sleep paralysis) along with a time frame for occurrences of these experiences ranging from within past month to lifetime and frequency within the time frame ranging from occasionally to almost every night (Fulda et al., 2008)

9.5.1.2.3 BECK DEPRESSION INVENTORY - II

The BDI-II is a 21-question multiple-choice self-report questionnaire that subjects will use to rate the presence, frequency, and severity of symptoms of depression using a 4-point Likert scale (Beck, et al., 1961). Scores on the BDI-II may range from 0 to 63, with higher scores indicating higher levels of depressive symptoms. Subjects with BDI-II scores greater than 19 will be excluded from participation.

9.5.1.2.4 BECK ANXIETY INVENTORY

The BAI is a 21-question multiple-choice self-report inventory that subjects will use to rate the presence, frequency, and severity of symptoms of anxiety using a 4-point Likert scale (Beck, et al., 1988). Scores on the BAI may range from 0 to 63, with higher scores indicating higher levels of anxiety symptoms. Subjects with scores on the BAI greater than 15 will be excluded from participation.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 POLYSOMNOGRAPHY

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

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

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

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per TIB, calculated as TST/interval from "lights off" until "lights on"
- WASO: minutes of wake from the onset of persistent sleep until lights on
- WASO2H: minutes of wake during the interval from 240 minutes after lights off until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least 1 epoch of wake, after onset of persistent sleep, and including any terminal awakening

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

- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening cannot be interrupted by stage N1, but must be interrupted by stage N2, N3, or REM
- Number of long awakenings
- Percentage of sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of persistent sleep to first epoch of REM

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

9.5.1.3.2 ELECTRONIC SLEEP DIARY

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-Up Period. This diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety.

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

Sleep Parameters

- Subjective Sleep Onset Latency (sSOL): estimated minutes from the time that the subject attempts attempting to sleep until sleep onset
- Subjective Wake After Sleep Onset (sWASO): sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stops trying to sleep for the night
- Subjective Total Sleep Time (sTST): derived minutes of sleep from sleep onset until the time the subject stops trying to sleep for the night
- Subjective Sleep Efficiency (sSE): proportion of sTST per subjective time spent in bed (sTIB), with sTIB calculated as the interval from the time that subject reports attempting to sleep until the time the subject stops trying to sleep for the night, and time spent asleep derived from sTIB minus sWASO

Quality of Sleep

The Sleep Diary will also include items assessing sleep quality and morning sleepiness/alertness.

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

Morning Sleepiness

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

The morning sleepiness question that is part of the electronic Sleep Diary will also be asked verbatim, using a paper-and-pencil format, at 1.5 hours after waketime each morning the subjects is in the clinic following a PSG recording. The rating on this question will be taken

into consideration by the investigator when making the determination about whether it is safe for the subject to be discharged from the clinic.

Alcohol Consumption

The Sleep Diary will include questions to determine whether or not the subject consumed alcohol the previous day within 3 hours before bedtime or exceeded the daily maximum of 2 alcoholic drinks.

9.5.1.3.3 INSOMNIA SEVERITY INDEX

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

9.5.1.3.4 FATIGUE SEVERITY SCALE

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS score is the sum of all responses to the 9 questions (Schwartz et al., 1993). Higher scores indicate greater fatigue.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

At predefined visits, a single, 4-mL blood sample per timepoint to determine plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) or zolpidem will be taken and will be processed according to instructions in a laboratory manual to be provided to the study sites. Plasma concentrations will be using validated liquid chromatography-tandem mass spectrometry assay methods. Concentrations of zolpidem will be determined only on an as needed basis as determined by the Study Director or Medical Monitor. The time and date of the 2 most recent doses preceding the samples obtained on Day 2 and Day 30 will be documented in the eCRF.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Postural Stability using the CDR Posture Assessment

Postural stability will be assessed using an apparatus similar to the Wright ataxiameter, and referred to as the CDR posture device. This device measures directional trunk movements (ie, body sway) through a cord placed around the subject's waist and connected to the ataxiameter. Subjects will stand on a firm surface with feet comfortably apart, either barefoot or wearing socks. The standing position and barefoot/socks conditions will be the

same for a given subject at each postural stability assessment timepoint. They will be instructed to stand as still as possible with eyes closed for 1 minute. On the evening of the Screening PSG visit, subjects will be introduced to the CDR posture assessment. On the morning after the Screening PSG, subjects will complete a CDR posture assessment session for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, starting within 5 minutes of morning waketime, at bedside) as during the testing sessions at subsequent visits.

Body sway is detected through the cable around the subject's waist by the ataxiameter and these data are transmitted to a laptop. Body sway is measured in units of 1/3° of the angle of arc. For ease in reporting these will be called arbitrary units, with a higher number indicating more body sway (less postural stability).

Cognitive Performance Assessment Battery

A computerized PAB will be administered on a laptop computer after the postural stability test. All tasks require a Yes/No button-press response. While completing the PAB, subjects will be in bed and ambient lighting will be maintained at a level of 80 to 100 lux at the subject's eye level. On the evening of the Screening PSG visit, before bedtime, subjects will be introduced to the PAB tasks and will undergo a minimum of 2 training sessions. If subjects cannot adequately perform the tasks during the training sessions, they will be excluded from further participation. On the morning after the Screening PSG, subjects will complete a session of the cognitive PAB for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, lighting, subject in bed) as during the testing sessions at subsequent visits.

The PAB comprises 9 tasks, including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Word Recognition, Picture Recognition, Numeric Working Memory, and Spatial Working Memory. The full PAB will take approximately 18 minutes to complete. Four composite domain factor scores are calculated by combining outcome variables from the various tests, as described below:

- Power of Attention
    - A composite score from the speed scores of 3 tests of attention
    - Reflects the ability to focus attention and process information

- Continuity of Attention
    - A composite score created by combining the accuracy scores from the tests of attention
    - Reflects the ability to sustain attention (vigilance)

- Quality of Memory
    - A composite score created by combining the accuracy measures from the two tests of working memory and the four tests of episodic memory

  - Reflects the ability to store information in memory and subsequently retrieve it
- Speed of Memory Retrieval
  - A composite score created by combining the reaction time scores from the two working memory tests and the two episodic recognition tests
  - Reflects time taken to retrieve information held in both working and episodic memory

9.5.1.4.3 PHARMACOGENOMIC ASSESSMENTS

Not applicable

9.5.1.4.4 OTHER BIOMARKER ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, and at the EOS Visit.

9.5.1.5.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

Suicidality will be assessed using a self-rated electronic version of the eC-SSRS (Posner et al., 2011). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Qualified personnel must evaluate positive responses on the eC-SSRS and take appropriate action as detailed in the training and certification process for administering the eC-SSRS.

9.5.1.5.2 TYRER BENZODIAZEPINE WITHDRAWAL SYMPTOM QUESTIONNAIRE

An assessment of withdrawal symptoms will be made using the T-BWSQ (Tyrer et al., 1990) to be completed at the EOS Visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes – moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's score. Scores above 20 will be considered clinically significant. Symptoms on the T-BWSQ will be analyzed and presented separately from AEs in the clinical study report.

9.5.1.5.3 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 observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Serious adverse events (SAEs) will be collected for 28 days after the last dose.

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

Abnormal ECG (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 QTc interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the eC-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5 for a description of the eC-SSRS).

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

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first.

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

ASSESSING SEVERITY OF ADVERSE EVENTS

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

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.4) for the definition of an SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

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

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

CLASSIFICATION OF CAUSALITY

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

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

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

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

9.5.1.5.4 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

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

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

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

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

The following hospitalizations are not considered to be SAEs because there is no "AE" (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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.5 LABORATORY MEASUREMENTS

Clinical laboratory tests are to be performed according to the schedule in Table 2. Blood and urine samples will be collected for the clinical laboratory tests as listed in Table 3. Subjects should be in a seated or supine position during blood collection.

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

Table 2 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 parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, globulin, glucose, iron, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Table 3 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments

	Volume per Sample Collection (mL)	Collection Time Points	Window Around Time Point	Volume Collected (mL)
Clinical laboratory tests	12[a]	Screening Baseline Day 31 EOS/ET	n/a	48
Viral tests	6[a]	Screening	n/a	6
PK sampling	4	Day 2 pm Day 3 am Day 30 pm Day 31 am	pm: within 2 hours predose am: after PAB and within 1 hour after morning waketime	16
Total Volume Collected				**70**

EOS = end of study, ET = early termination, n/a = not applicable, PK = pharmacokinetic

a. Estimated volume.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or two 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 9.5.1.5.3) and the case report form (CRF) Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs, the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Reporting of Serious Adverse Events, Section 9.5.4.1).

9.5.1.5.6 VITAL SIGNS AND WEIGHT MEASUREMENTS

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

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

9.5.1.5.7 PHYSICAL EXAMINATIONS

Physical examinations (full or brief) will be performed as designated in the Schedule of Procedures/Assessments Table 4). At Screening and at the end-of-study visit, a full physical examination will be conducted, including evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin. The full physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). A urogenital examination will only be required in the presence of clinical symptoms related to this region and at the discretion of the investigator. At other study visits as designated in Table 4, a brief physical examination will be conducted to assess health status by brief evaluation of the head, eyes, ears, nose, throat, heart, lungs, abdomen, and extremities, and other physical conditions of note. Documentation of the physical examinations, including the brief neurological examinations, will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE eCRF.

9.5.1.5.8 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 4).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.3). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.4), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

OTHER ASSESSMENTS

EQ-5D-3L

The EQ-5D-3L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility (The Europol Group, 1990; Brooks et al., 1996). The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 (“Worst imaginable health state”) to 100 (“Best imaginable health state”).

PATIENT GLOBAL IMPRESSION – INSOMNIA

The PGI-Insomnia questionnaire is a self-report assessment asking about a subject's perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a: helped/worsened sleep, b: decreased/increased time to fall asleep, and c: increased/decreased TST) and 1 item related to perceived appropriateness of study medication strength. The first 3 items are answered on a 3-point scale (1=positive medication effect, 2=neutral medication effect, 3=negative medication effect) and the last item on a different 3-point scale (medication: 1=too strong, 2=just right, 3=too weak). Each item will be reported separately. This scale was used in studies of zolpidem (Roth et al., 2006; Walsh et al., 2008).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

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

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-7	-3		-3		-3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-28 to -17	-17 to -14	-16 to -13	-10 to -7	-9 am to -6 am	-9 pm to -6 pm	-8 to -5	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
Demographics	X																			
Informed consent	X																			
Inclusion/exclusion criteria[f]	---------->																			
Height	X																			
Weight	X							X								X		X	X	
Clinical laboratory tests	X							X								X		X	X	X
Viral screening	X																			
Vital signs	X							X								X		X	X	X
12-lead ECG	X							X								X		X	X	X
Sleep, medical, and psychiatric history	X																			
ISI	X			X				X								X				
SDSB[g]	X																			
Physical exam[h]	X															X		X	X	X
Prior / concomitant medications	---------->																	---------->		

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-7	-3		-3		-3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-28 to -17	-17 to -14	-16 to -13	-10 to -7	-9 am to -6 am	-9 pm to -6 pm	-8 to -5	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
Beck Depression Inventory II	X																			
Beck Anxiety Inventory	X																			
Urine drug test	X	X		X		X		X			X		X		X					X
Postural stability		X[i]	X[j]		X		X			X		X		X		X				
Cognitive PAB		X[i]	X[j]		X		X			X		X		X		X				
FSS	X			X				X								X				
Morning Sleepiness			X		X		X			X		X		X		X				
Sleep Diary[k]		----------															--------->			
EQ-5D-3L	X			X				X								X				
PK blood sampling[l]											X	X			X	X				X
eC-SSRS	X							X				X				X		X	X	X
Polysomnography[m]			X		X		X			X		X		X		X				
Randomization									X											
PGI-Insomnia																X				

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-7	-3		-3		-3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-28 to -17	-17 to -14	-16 to -13	-10 to -7	-9 am to -6 am	-9 pm to -6 pm	-8 to -5	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
T-BWSQ																		X	X	
Dispense study drug			X									X								
Study drug at bedtime[n]		---------->																		
Retrieve unused study drug								X					X							
Check study drug compliance[o]				X				X					X							
Admission to clinic		X		X		X		X			X		X		X					
Discharge from clinic			X		X		X			X		X		X		X				
Discharge from study																		X	X	
Adverse events	---------->																			

Table 5 Schedule of Procedures/Assessments in Study E2006-G000-304

BL = baseline, eC-SSRS = electronic Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EMG = electromyography, EOS = end of study; ET = early termination, FSS = Fatigue Severity Scale, ISI = Insomnia Severity Index, PAB = performance assessment battery, PGI = Patient Global Impression, PK = pharmacokinetic, PSG = polysomnography, SDSB = Sleep Disorders Screening Battery, T-BWSQ = Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; UN = unscheduled visit.

a: Must be consecutive with Visit 3a.
b: Must be consecutive with Visit 5b.
c: Must be consecutive with Visit 7a.
d: Must occur 14 – 18 days after Visit 8.
e: Subjects who discontinue the study early for any reason after Randomization at Visit 5 should complete this visit.
f: Inclusion and exclusion criteria to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2.
g: The Sleep Disorders Screening Battery includes: STOPBang, International Restless Legs Scale, Epworth Sleepiness Scale, and Munich Parasomnia Scale.
h: Full physical examination (including a brief neurological exam) will be carried out at Screening and EOS and ET (if applicable). Brief physical examinations will be carried out at other visits.
i: For training purposes only. Introduction to the CDR posture assessment and at least 2 training sessions of cognitive PAB to be completed during Visit 2a.
j: For familiarization purposes only. The CDR posture and cognitive PAB assessments are to be completed at Visit 2b under the same conditions as for testing at subsequent visits.
k: Should be completed, within 1 hour of morning waketime, on every day of the study from Screening until the end of the study, and reviewed for eligibility before initiating any study assessments at Visit 2 and Visit 3.
l: One PK blood sample (approximately 4 mL) will be obtained at the following timepoints: within 2 hours predose Day 2 and Day 30; within 1 hour after morning waketime on Day 3 and Day 31.
m: PSG recordings will include a standard montage on all PSG nights. Diagnostic channels (respiratory effort, airflow, leg EMG) will be added to the standard montage on the PSG at Visit 2.
n: First dose of study drug on night at home after Visit 2b. On the days that subjects are admitted to the clinic, study drug will be administered to the subject by clinical staff. On days that the subjects are not admitted to the clinic subjects will self-administer study drug. All study drug administration must be within 5 minutes of bedtime (defined as the time the subject attempts to sleep).
o: Subjects will be questioned about study drug compliance upon check-in at Visits 3a, 5a, and 7a. Tablet counts study drug compliance will be done after end of Run-in Period and end of Treatment Period.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

Most of the clinical assessments are standard measurements commonly used in studies of drugs for the treatment of subjects with insomnia disorder.

Completion of sleep diaries by subjects is considered to be an appropriate method to measure changes in subjective sleep parameters, thereby allowing assessments of secondary efficacy in this study. The advantages of the electronic Sleep Diary to be used in this study include that the questions and instructional text have been adapted from sleep diaries that have were developed by clinicians and researchers with expertise in insomnia disorder, and have undergone linguistic validation and cognitive debriefing to optimize their use in this study. The Sleep Diary will include questions to assess the subject's rating of sleep quality each night and sleepiness/alertness level in the morning. The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. The FSS measures fatigue, which is another type of daytime impairment that is often a consequence of insomnia. This scale has been employed primarily in clinical trials of cognitive and behavioral treatments for insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of both nighttime sleep and daytime impairment complaints, the ISI and the FSS will be evaluated for changes from baseline. The PGI-Insomnia and EuroQoL assessment (version EQ-5D-3L) will also be employed. Both measures have been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life. Together these measures will provide a broad evaluation of the effects of lemborexant on each patient's sleep, daytime functioning, and quality of life.

The CDR posture and cognitive PAB will assess whether there are residual effects of study drug on morning postural stability and cognition. There are documented effects of hypnotic drugs, including zolpidem, on postural stability and certain cognitive domains in the morning hours. These effects are associated with an increased risk of falling and other negative effects on functioning in the morning hours. The measures to be employed to evaluate the effects on postural stability and cognition have been widely used in clinical trials of drugs in older individuals, including clinical trials of treatments for insomnia disorder.

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

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

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

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

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

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

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Although the female subject population will be postmenopausal, in the event that a pregnancy does occur, investigators will capture and report such events.

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

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

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see 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 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies

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

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

9.5.4.3 Reporting of Events Associated with Special Situations

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. Investigators should report whether one or both study drugs had been taken incorrectly. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) 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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

For analysis purposes, a subject will be considered to have completed the study once the assessments on the morning after the last dose of study drug have been completed. All subjects will be required to return to the clinic at least 14, but not more than 18 days later for an End of Study (EOS) visit.

The investigator or subject may elect to discontinue the subject's participation in the study at any time for any reason. Subjects who discontinue study drug prematurely at any time after randomization at Visit 3 (Study Baseline) will be encouraged to return to the site as soon as possible (preferably within 7 days) to undergo an early termination (ET) Visit, as described in the Schedule of Procedures/Assessments (Table 4).

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

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, lack of therapeutic effect, or administrative/other. Discontinuations due to non-compliance with study drug, time spent in bed, or alcohol restrictions will be assigned to "administrative/other." In addition to the primary reason, the subject may indicate one or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason will not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of one or both study drugs.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.4. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 must sign the completed eCRF 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 eCRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required.

The statistical analyses are described in this section. Further details of the statistical analyses will be included in a separate SAP.

All statistical tests will be based on the 5% level of significance (two-sided). If statistical comparisons are not defined, all pairwise comparisons will be tested.

9.7.1.1 Study Endpoints

Unless otherwise stated, the time points for Sleep Diary endpoints refer to the mean of the final 7 nights before the visit.

9.7.1.1.1 PRIMARY ENDPOINT(S)

The primary endpoint is:

- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 compared to ZOL

9.7.1.1.2 SECONDARY ENDPOINT(S)

Key Secondary Endpoints

- Change from baseline of mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL

- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL

Additional Secondary Endpoints

- Change from baseline of mean LPS, SE, WASO, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL

- Change from baseline of mean subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL

- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to PBO

- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO

- Proportion of responders on Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that

    - Objective sleep onset response is defined as LPS ≤ 20 minutes (provided mean baseline LPS was > 30 minutes)

    - Subjective sleep onset response is defined as sSOL ≤ 20 minutes (provided mean baseline sSOL was > 30 minutes)

    - Objective sleep maintenance response is defined as WASO ≤ 60 minutes (provided mean baseline WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)

    - Subjective sleep maintenance response is defined as sWASO ≤ 60 minutes (provided mean WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)

- Safety and tolerability of LEM

- Change from baseline of the score from items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO

- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO

- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

9.7.1.1.3 EXPLORATORY ENDPOINT(S)

The following endpoints will be explored for LEM10 and LEM5. Except for PK endpoints, comparisons to ZOL and PBO will be made.

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period

- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31

- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO

- Rebound insomnia endpoints as assessed from the Sleep Dairy during the Follow-up Period

    - Change from baseline of sSOL on each of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period

    - Change from baseline of sWASO on each of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period

    - Proportion of subjects whose sSOL is longer than at baseline for each of the first 3 nights, or whose mean sSOL is longer than at baseline for first 7 nights or second 7 nights of the Follow-up Period

    - Proportion of subjects whose sWASO is higher than at baseline for each of the first 3 nights, or whose mean sWASO is higher than at baseline for the first 7 nights or second 7 nights of the Follow-up Period

- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period

- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period

- Change from baseline of mean minutes and mean percentage (a) per TIB and (b) per TST of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30

- Change from baseline of mean of median REM latency, mean number of awakenings, and mean number of long awakenings at Days 1 and 2 and Days 29 and 30

- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31

- Change from baseline on the EQ-5D-3L at Day 31

- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study

- Proportion of subjects who score ≥ 3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study

- PK of lemborexant and its metabolites M4, M9, and M10

- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

9.7.1.2 Definitions of Analysis Sets

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

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

The Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the SAP.

The PK Analysis Set is the group of subjects who have at least one quantifiable plasma concentration of lemborexant or its metabolites, or zolpidem, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least one quantifiable lemborexant concentration data point as per the PK Analysis Set.

9.7.1.3 Subject Disposition

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

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and BMI; categorical variables include sex, age group (55-64 years; 65 years or older), BMI group (less than 18.5, 18.5 to less than 25, 25 to 30, above 30), race and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using Sleep Diary variables including sSOL, sWASO, sSE and sTST; PSG variables including LPS, WASO, SE, WASO2H and TST; ISI score and its individual question score, and FSS. The BDI-II and BAI scores will also be summarized at Study Baseline.

The above tables will be produced for the FAS if it differs from the Safety Analysis Set.

If sufficient numbers of subjects with a particular medical history (major depression, anxiety disorder, chronic pain, etc) are enrolled, demographic and other baseline characteristics will be summarized for each medical history group using descriptive statistics.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (Mar 2016 or latest version). The number (percentage) of subjects who take prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary-preferred term (PT). If the Safety Analysis Set and FAS differ substantially, then the prior and concomitant medication summaries will be repeated on the FAS.

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

Concomitant medications are defined as medications that (1) started before the first dose of study drug (including PBO Run-In Period) 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 (including the PBO Run-In Period) to the last dose day plus 14 days. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Where Sleep Diary endpoints are described, the first 7 nights of treatment refer to diary data entered on the first 7 mornings following the start of treatment; the last 7 nights of treatment refer to diary data entered on the last 7 mornings (up to and including the morning following the last PSG). Details of the handling of missing data for the various assessments will be addressed in the SAP.

Where PSG endpoints are described, Days 1 and 2 refer to the first two PSG recordings after start of treatment (scheduled on Visits 5 and 6), and Days 29 and 30 refer to the last two PSG recordings of the Treatment Period (scheduled on Visits 7 and 8).

Definition of Baseline

Baseline is defined as the means from the 2 PSGs during the Run-in period for PSG-derived variables; and the mean of the last 7 mornings before the first Baseline PSG during the Run-In Period for Sleep Diary variables. For other endpoints, baseline data are captured during the Run-in Period and Baseline Period. Details will be specified in the SAP.

Control of Type I Error

A sequential gate-keeping procedure including the primary endpoint comparison (WASO2H of LEM10 vs ZOL) and the key secondary efficacy endpoint comparison (WASO2H of LEM5 vs ZOL) at Month 1 will control for type I error. In order to proceed from one step to the next the outcome must be significant at 0.05 (two-sided).

- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM5 compared to ZOL

This testing procedure controls the overall type I error rate of 0.05.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Null Hypothesis: No difference exists in the mean change from baseline of the mean WASO2H of Days 29 and 30 for treatment with LEM10 as compared with ZOL.

Alternative Hypothesis: A difference exists in the mean change from baseline of the mean WASO2H of Days 29 and 30 for LEM10 compared to ZOL.

The WASO2H change from baseline (the mean of Days 1 and 2, and the mean of Days 29 and 30) will be analyzed using longitudinal data analysis (LDA) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), country, age group (55-64 years; 65 years or older), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The LDA model accounts for any missing data, and assumes that the missing data are missing at random. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. Provided that the data are normally distributed, least square (LS) means, difference in LS means of lemborexant dose compared to ZOL and PBO, 95% confidence intervals (CIs), and P-values will be presented. The primary comparison will be to compare the mean of Days 29 and 30 of LEM10 to ZOL; a key secondary comparison is to compare the mean of Days 29 and 30 of LEM5 to ZOL. Other pairwise comparisons comparing Days 1 and 2 of LEM10 and LEM5 to ZOL, comparing LEM10 and LEM5 to PBO at both time points are secondary.

Additional analyses will include investigating subgroup analyses and/or addition of covariates to the model of age, sex, race, BMI, country and/or other subgroups to be determined before unblinding.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Changes from baseline of mean units of body sway of the mean of Days 2 and 3 and the mean of Days 30 and 31 will be analyzed using the same LDA method as the primary endpoint. Where data are normally distributed, LS means, difference in LS means of LEM10 and LEM5 compared to ZOL and compared to PBO, 95% CIs and P -values will be presented for each time point. Corresponding to the key secondary objective, the key secondary comparisons will be to compare body sway on Days 2 and 3 of LEM10 and LEM5 to ZOL. The means of Days 30 and 31 comparing LEM5 and LEM10 to ZOL and PBO will be exploratory.

Using the same LDA method as for the primary endpoint, the secondary efficacy endpoints (change from baseline of the mean of the following endpoints: WASO2H of the mean of Days 1 and 2; WASO, LPS, SE, and TST of the mean of Days 1 and 2 and of the mean of Days 29 and 30; sSOL, sWASO, sSE, and sTST for the mean of the first 7 and last 7 days of the Treatment Period) will be analyzed. Corresponding to the secondary objectives, appropriate pair-wise treatment comparisons will be made. Where data are normally distributed, LS means, difference in LS means of each lemborexant dose compared to ZOL and compared to PBO, 95% CIs and P-values at the appropriate time point will be presented.

The proportion of responders after the first 2 and last 2 nights of treatment based on PSG variables (WASO and LPS, respectively) will be analyzed using the Cochran-Mantel-Haenszel test, controlled for country and age group, for each dose of lemborexant compared to PBO and ZOL. The analysis will be similarly repeated for responder analysis based on Sleep Diary variables (sSOL and sWASO) over the first 7 and last 7 nights of treatment.

The change from baseline of the ISI total of four items on daytime functioning at Day 31 and the FSS score at Day 31 will be analyzed using analysis of covariance (ANCOVA), adjusted for the corresponding baseline value, age group, country, and treatment.

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

9.7.1.6.3 Exploratory Efficacy and Pharmacodynamic Analyses

The change from baseline mean score of the quality of sleep item on the Sleep Diary for the means of the first 7 days and last 7 days of the Treatment Period will be analyzed using the same LDA method as the primary efficacy endpoints.

Changes from baseline in mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval for the PAB tasks will be analyzed similarly to the primary efficacy endpoints to compare each dose of lemborexant to ZOL and to PBO.

Rebound insomnia will be addressed by comparing Sleep Diary data (sSOL and sWASO) from each of the first 3 mornings, the first week, and the second week of the Follow-up Period with Sleep Diary data during the Screening Period. These data will be analyzed using ANCOVA, adjusted for country, age group and treatment. Rebound Insomnia will be defined as present if the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group. In addition, the proportion of subjects whose sSOL or sWASO on each of the first 3 nights and each of the 2 weeks of the Follow-up Period exceeds the subject's value on that parameter during the Screening Period will be summarized by treatment group.

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-up Period will be analyzed using the same LDA method as the primary efficacy endpoints.

The change from baseline of the mean of Days 1 and 2 and of the mean of Days 29 and 30 for the sleep architecture and other PSG endpoints (minutes and percentage [a] per TIB and [b] per TST of sleep stage N1, N2, N3, total NREM and REM; REM latency, DurLongAW, number of awakenings, number of long awakenings, REM episode frequency and duration, and mean REM/NREM cycle duration) will be analyzed as per the primary efficacy analyses.

Each item on the PGI-Insomnia at Day 31 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

The change from baseline in the EQ-5D-3L score at Day 31 will be analyzed using ANCOVA, adjusted for country, age group and treatment.

Additional exploratory endpoints may be evaluated to facilitate understanding study data and interpret study results.

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, as well as zolpidem (where quantified) plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and its metabolites M4, M9, and M10, as well as zolpidem (where quantified) plasma concentrations by dose, time and day.

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK analysis data from this study will be pooled with relevant data from Phase 1 and 2 studies, and other Phase 3 studies if available. To explore sources of variability in lemborexant PK, the effect of covariates (eg, demographics) on the PK of lemborexant will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC, $C_{max,}$ and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic Analyses

These analyses are described in the Secondary Efficacy Analyses, and Exploratory and Pharmacodynamic Analyses sections (above).

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship between exposure to lemborexant and efficacy variables including but not limited to LPS and WASO, and safety variables including but not limited to morning sleepiness and frequently occurring treatment-emergent adverse events (TEAEs), will be explored graphically. Any emergent PK/PD relationships will be evaluated by population

PK/PD modeling. The population PK/PD analysis plan will be described and results will be reported in a separate document.

Population PK and PK/PD analyses will be performed using NONMEM version 7.2 or later.

Pharmacogenomic Analyses

Not applicable

Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

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, separately for each type of tablet. 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 eCRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings. AEs will be classified as TEAEs up to 14 days after the last study treatment.

Adverse events will be summarized by descriptive statistics, using the Safety Analysis Set. The TEAEs will be summarized by treatment group at the start of the TEAE. 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 during the Run-In Period will be summarized separately. The number (percentage) of subjects with TEAEs during the Treatment Period will be summarized separately. 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]). Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

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

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

The number (percentage) of subjects with TEAEs of cataplexy or that are characterized according to the customized MedDRA query PT as potential cataplexy-related events, as well as somnolence and related events, and drug abuse liability will be summarized separately.

9.7.1.8.3 CLINICAL LABORATORY VALUES

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

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

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

9.7.1.8.4 VITAL SIGNS, HEIGHT, AND WEIGHT

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from Study Baseline will be presented by visit and treatment group. Height will be measured once at Visit 1.

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range (Table 6). Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented for change from Study Baseline, by treatment group and by time point.

Table 6 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

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

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

9.7.1.8.6 OTHER SAFETY ANALYSES

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning residual sleepiness item on the

Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of each of the 2 weeks after treatment discontinuation will be analyzed using the same LDA method as the primary efficacy endpoints.

The results of eC-SSRS assessments will be listed for each subject. The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group using descriptive statistics as appropriate.

Withdrawal symptoms will be assessed using the T-BWSQ. The mean score will be summarized by treatment group, and number (percentage) of subjects with a score ≥3 will be summarized.

Urine drug test results will also be listed.

9.7.1.9 Other Analyses

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

Although zolpidem is included in the study as an active comparator, comparison of ZOL to PBO, and comparison between LEM10 and LEM5 may be made to facilitate evaluation of study results.

9.7.2 Determination of Sample Size

The sample size was estimated for the comparison of LEM10 with ZOL with respect to the mean change from baseline of WASO2H at Month 1, on the basis of a two-sided test at the 0.05 α-level.

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the SD of change from baseline for WASO2H is assumed to be 38 minutes. The LS mean treatment difference at Days 14/15 from Study 201 for WASO2H of LEM10 compared with PBO was -11 min. On the basis of the FDA Center for Drug Evaluation Research Statistical Review of Ambien CR (zolpidem tartrate extended release/modified release) New Drug Application filing, ZOL may have approximately -1 to -2 minutes treatment effect on WASO2H compared to PBO if ZOL is dosed at bedtime. Therefore, assuming a treatment difference in WASO2H of -10 minutes, a sample size of 250 per treatment group at 5% (2-sided) level of significance has 84% power for comparing LEM10 with ZOL.

Power is also estimated for the key secondary objective, the comparison of LEM5 and LEM10 to ZOL on postural stability in the morning. For the assessment of postural stability using body sway, a 7-unit difference between active treatment and PBO with respect to change from time-matched baseline data is proposed to be clinically meaningful (Wesnes, et al, 2000). A difference of 7 unit represents a 35% change relative to placebo, which has been suggested to be a minimally clinically meaningful increase in body sway that is associated with a blood alcohol level of 0.5 g/L (Jongen, et al., 2014) and an increased risk of falling (eg, Mets, et al., 2010). Assuming a treatment difference of 3.5 units and SD=12, a sample

size of 250 per treatment group at 5% (2-sided) level of significance has 90% power for detecting a statistically significant difference between LEM and ZOL.

9.7.3 Interim Analysis

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the conditional power will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved with the conduct of the study will have access to the interim data or the results of the interim analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis is concluded.

9.7.4 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

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eC-SSRS Reference

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

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to 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 (or if regionally required, the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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 and remote monitoring will be conducted between onsite monitoring visits by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, 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 eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

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, sonograms, computerized tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
    - Pain, quality of life, or medical history questionnaires completed by subjects
    - Records of telephone contacts
    - Diaries or evaluation checklists
    - Drug distribution and accountability logs maintained in pharmacies or by research personnel
    - Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
    - Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
    - eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

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

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

11.5 Identification of Source Data

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated

representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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

11.7 Auditing Procedures and Inspection

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

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, 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; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

Sponsor's Grading for Laboratory Values

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 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.

Schedule of Inclusion/Exclusion Criteria Assessments

Visit Name	V1	V2	V3	V4	V5
	Screening	**Screening 1 PSG1**	**Screening 2/ Baseline 1 PSG2**	**Screening 3/ Baseline 2 PSG2**	**Day 1 am**
Inclusion Criterion Number	I1, I2, I3, I4, I5, I6, I14, I15	I7, I8, I9	I3, I10, I11, I12, I13	I13	-
Exclusion Criterion Number	E1, E2, E3, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E22, E23, E24, E25, E26, E27, E28	E4, ,E22, E23, E24, E25	E22,E23, E24, E25	E22, E25,	, E22,E23, E24, E25

PSG = polysomnography, V = visit

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	o Barbiturates o Benzodiazepines o GABA analogues o Hydantoins o Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter)	o Diphenhydramine HCl o Carbinoxamine o Doxylamine o Dimenhyrinate o Triprolidine o Bromopheniramine o Chlorphemamine o Hydroxazine
Antihistamines with known sedating effects	o Non-sedating, eg, Claritin™ is not prohibited
Anxiolytics with known sedating effects	o Lorazepam o Alprazolam o Buspirone
Strong CYP3A inhibitors	o Amiodarone o Cimetidine o Clarithomycin o Diltiazem o Erythromycin o Fluvoxamine o Itraconazole o Ketoconazole o Mibefradil o Nefazodone o Troleandomycin o Verapamil

Category	Medication
Moderate CYP3A inhibitors	o Amiodarone o Cimetidine o Clarithromycin o Diltiazem o Erythromycin o Fluvoxamine o Itraconazole o Ketoconazole o Mibefradil o Nefazodone o Troleandomycin o Verapam
CYP3A inducers	o Carbamazepine o St. John's Wort o Phenobarbital o Troglitazone o Phenytoin o Rifabutin o Rifampin
Hypnotics	o Melatonin o Prescribed or OTC
Herbal preparations with sedating effects	-
MAOIs	-
Opioid Analgesics	-
Muscle relaxants (centrally-acting) with known sedating effects	o GABA analogues o Hydantoins o Phenyltriazines
Stimulants	o Amphetamines o Modafinil o Armodafinil o Methylfenidate
Other	o Warfarin, heparin, ticlopidine o Non-stimulant diet pills o Systemic isoretinoin o Systemic glucocorticoids o Glucose metabolizing agents o Tryptophan

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant
IND Number:	111,871
EudraCT Number:	2015-004347-39

SIGNATURES

Authors:

Patricia Murphy, PhD Study Director Associate Director, Clinical Research Neuroscience and General Medicine Product Creation Unit Eisai Inc.	Date
Luigi Giorgi, MD Medical Monitor Executive Director Neuroscience and General Medicine Product Creation Unit Eisai Ltd.	Date
Ishani Savant Landry, PhD Clinical Pharmacologist Director, Clinical Pharmacology and Translational Medicine Neuroscience and General Medicine Product Creation Unit Eisai Inc.	Date
Quan Hong, PhD Biostatistician Director, Biostatistics Neuroscience and General Medicine Product Creation Unit Eisai Inc.	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant
IND Number:	111,871
EudraCT Number:	2015-004347-39

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

Medical Institution

Investigator	Signature	Date

Revision History:
Previous Version (Amendment 03): V6.0
Current Version (Amendment 04): V7.0
Date of Revisions: 05 Feb 2018

Change	Rationale	Affected Protocol Sections
Revised order of key secondary objectives and related endpoints	To incorporate feedback from regulatory authorities	Synopsis – Objectives Synopsis – Statistical Methods Synopsis – Sample Size Rationale Section 8.2.1 Section 9.7.1.1.2 Section 9.7.1.6 Figure 2 Section 9.7.1.6.2 Section 9.7.2
Added sensitivity analysis	To incorporate feedback from regulatory authorities	Section 9.7.1.6.1
Revised process for Control of Type I Error	To align with revised order of objectives and endpoints	Section 9.7.1.6
Revised age ranges for categorical variables	Correction	Synopsis – Statistical Methods Section 9.7.1.4 Section 9.7.1.6.1

Revision History: Previous Version (Amendment 02): V5.0 Current Version (Amendment 03): V6.0 Date of Revisions: 16 Jun 2017		
Change	**Rationale**	**Affected Protocol Sections**
Revised order of Primary, Key Secondary, Additional Secondary, and Exploratory objectives and related endpoints	To incorporate feedback from regulatory authorities	Synopsis – Objectives Synopsis – Statistical Methods Synopsis – Sample Size Rationale Section 7.2 Section 8.1 Section 8.2 Section 8.3 Section 9.2.2 Section 9.2.3 Section 9.2.7 Section 9.7.1.1.1 Section 9.7.1.1.2 Section 9.7.1.1.3 Section 9.7.1.6.1 Section 9.7.1.6.2 Section 9.7.1.6.3 Section 9.7.1.8.6 Section 9.7.2
Revised process for Control of Type I Error	To align with revised order of objectives and endpoints	Synopsis – Statistical Methods Section 9.7.1.6
Added WASO1H as a sleep architecture parameter (efficacy)	Correction	Synopsis – Assessments Section 9.5.1.3.1
Revised description of mornings sleepiness scale	Correction	Section 9.5.1.3.2
Revised age groups for analysis	In response to request from regulatory authorities	Section 9.7.1.4
Revised analysis covariate from country to region	To ensure adequate number of subjects per analysis group	Throughout
Revised Sponsor Signature Page	To reflect current sponsor signatories	Sponsor Signature Page

Revision History: Previous Version (Amendment 01): V4.0 Current Version (Amendment 02): V5.0 Date of Revisions: 16 Feb 2017		
Change	**Rationale**	**Affected Protocol Sections**
Revised approximate number of sites from 90 to 105	To facilitate study enrollment	Synopsis – Site(s) Section 6 Section 9.3
Revised text to allow Sleep Diary entries may be to be maintained in paper format as a backup to the electronic Sleep Diary, if necessary	To allow flexibility in diary data collection in the event electronic diary is not available	Synopsis – Assessments Section 9.5.1.3.2
Revised to Screening Period from up to -28 days to up to -35 days	To allow flexibility in scheduling	Synopsis – Study Design Section 9.1 Section 9.1.1.1 Figure 1 Table 4
Revised total number of expected screened subjects from 2100 to 2800	To reflect current screen failure rate	Synopsis – Number of Subjects Section 9.3
Revised inclusion (#6) requirement for ISI at both V1 and V3 from "≥15" to "≥13".	To more accurately target study population (those with chief complaint of sleep maintenance insomnia) for inclusion	Synopsis – Inclusion Criteria Section 9.3.1
Revised inclusion (#9) requirements for time spent in bed requirement from ">9 hours on more than 2 nights per week" to ">10 hours on more than 2 nights per week.	To permit broader inclusion of appropriate subjects	Synopsis – Inclusion Criteria Section 9.3.1
Revised inclusion (#13) to eliminate the need for sleep efficiency component	For consistency throughout protocol	Synopsis – Inclusion Criteria Section 9.3.1
Revised exclusion (#1) for ESS score ">10" to ">15" as an indicator of excessive daytime sleepiness and required that scores of 11-15 require excessive daytime sleepiness to be recorded in subject's Medical History)	Based on ESS data in Study 304 to date, to record excessive sleepiness in medical history instead of excluding subjects	Synopsis – Exclusion Criteria Section 9.3.2 Section 9.5.1.2.1
Revised exclusion (#3) for MUPS such that endorsing	To allow investigatory follow-up and clinical	Synopsis – Exclusion Criteria

Revision History: Previous Version (Amendment 01): V4.0 Current Version (Amendment 02): V5.0 Date of Revisions: 16 Feb 2017		
Change	**Rationale**	**Affected Protocol Sections**
item relating to a history of symptoms of Rapid Eye Movement (REM) Behavior Disorder or sleep related violent behavior is no longer automatically exclusionary and clarified requirements with regard to sleep-driving	judgment for subjects who endorse the item regarding a history of "acting out dreams," rather than automatically excluding these subjects	Section 9.3.2
Revised exclusion (#19) for suicidal behavior as per the C-SSRS from a "lifetime" to "in the past 10 years"	To facilitate enrollment and align with other protocols in the program	Synopsis – Exclusion Criteria Section 9.3.2
Revised window around Screening and Run-In Visits	To permit flexibility in scheduling of subjects	Synopsis – Study Design Section 9.1.1.1 Section 9.1.1.2 Table 4
Revised timing for CDR posture training from "during" for "before" Visit 2a	To permit training on the assessment at Visit 1	Table 4
Revised analyses for Rebound Insomnia	To match final Study 303 protocol per VHP review	Synopsis – Statistical Methods Section 9.7.1.1.3 Section 9.7.1.6.3
Revised the detailed Inclusion/Exclusion Criteria Schedule (Appendix 2)	For clarity	Appendix 2
Revised List of Prohibited Concomitant Medications (Appendix 3)	To correct lists of strong and moderate CYP3A inhibitors and CYP3A inducers	Appendix 3
Deleted Zolpidem Prescribing Information (Appendix 4)	To ensure sites always have the most current approved version (will be provided to sites outside the protocol)	Section 9.4.1 Appendix 4
Added the requirement for monitoring of seizures and falls	Per request of FDA	Synopsis – Study Methods Section 9.2.5 Table 4
Revised text regarding ECG interpretation categories	For clarity	Section 9.7.1.8.5

Revision History: Previous Version (Amendment 01): V4.0 Current Version (Amendment 02): V5.0 Date of Revisions: 16 Feb 2017		
Change	**Rationale**	**Affected Protocol Sections**
Revised T-BWSQ assessment description such that scores above 20 will not be considered clinically significant and that the symptoms will no longer be summarized separately from all other AEs.	For clarity	Synopsis – Study Assessments Section 9.5.1.5.2
Revised Sponsor signature page	To reflect current Eisai personnel	Protocol Signature Page

Revision History:

Previous Version (Revised protocol): V3.0

Current Version (Corrected protocol): V4.0

Date of Revisions: 16 Jul 2016

Change	Rationale	Affected Protocol Sections
Corrected typographical errors in the list of exclusion criteria	For consistency and editorial quality. No changes to content.	Section 9.3.2

Revision History: Previous Version (Revised protocol): V2.0 Current Version (Amended protocol): V3.0 Date of Revisions: 24 Jun 2016		
Change	**Rationale**	**Affected Protocol Sections**
Stated in all relevant places in Study Design that subjects will rate their morning sleepiness at 1.5 hours after waketime, and specified analysis methods for this assessment	For consistency with Schedule of Assessments and completeness of analysis methods	Synopsis – Study Design Synopsis – Statistical Methods Section 9.1.2.1 Section 9.5.1.3.1 Section 9.7.1.1.3 Section 9.7.1.6.3
Specified that exclusion criteria include current diagnosis of obstructive sleep apnea	Per VHP comment	Synopsis – Exclusion Criteria Section 4 Section 9.3.2
Revised STOPBang score cutoff for exclusion from study	To avoid low specificity of more stringent criterion	Synopsis – Exclusion Criteria Section 9.3.2
Revised Epworth Sleepiness Scale score cutoff for exclusion from study	To avoid low specificity of more stringent criterion	Synopsis – Exclusion Criteria Section 9.3.2
Deleted “on a screening questionnaire” from exclusion criterion pertaining to screening for narcolepsy symptoms	No formal screening questionnaire is being utilized	Synopsis – Exclusion Criteria Section 9.3.2
Provided examples of clinically significant disease that would exclude the subject from the study	Per VHP review; to specify conditions for which zolpidem is contraindicated	Synopsis—Exclusion Criteria Section 9.3.2
Stated that subjects taking sedating drugs that would interfere with occupation or activities will be excluded	Per VHP review; to exclude such individuals from the study for reasons of safety	Synopsis – Exclusion Criteria Section 9.3.2
Revised the washout interval between taking a prohibited medication, including treatment for insomnia, and the first dose of study medication	For consistency and to account for medications or insomnia treatments with long half-lives	Synopsis – Exclusion Criteria Section 9.3.2 Section 9.4.7.2
Prohibited strong CYP3A inhibitors from being used any time during study, even if intermittently	Per VHP review; based on known drug metabolism interactions with zolpidem	Synopsis – Concomitant Drug Therapy Section 9.3.2 Section 9.4.7.2

Revision History: Previous Version (Revised protocol): V2.0 Current Version (Amended protocol): V3.0 Date of Revisions: 24 Jun 2016		
Change	**Rationale**	**Affected Protocol Sections**
Clarified that the MUPS to be used is an adapted version	For accuracy	Synopsis – Assessments Section 9.5.1.2.2
Added sleep onset latency as a PSG variable	For completeness of PSG variable dataset	Synopsis – Assessments Section 9.5.1.3.1
Clarified definition of REM latency	For accuracy	Synopsis – Assessments Section 9.5.1.3.1
Changed wording such that sleep diary will ask, not determine, alcohol consumption	For accuracy	Synopsis – Assessments Section 9.5.1.3.2
Allowed flexibility for the means of documenting the time and date of 2 most recent doses before each blood sample for pharmacokinetic analyses	Time and date are being documented by means other than in the electronic Case Report Form	Synopsis – Assessments Section 9.5.1.4.1
Clarified details of the CDR posture assessment at screening	For accuracy	Synopsis Assessments Section 9.5.1.4.2
Deleted statement that all cognitive performance assessment batteries require Yes/No button response	For accuracy – some tasks do not require a Yes/No button response	Synopsis – Assessments Section 9.5.1.4.2
Revised the expected completion time for the full PAB	For accuracy	Synopsis – Assessments Section 9.5.1.4.2
Moved analysis of cognitive PAB tasks from Exploratory to Secondary Analyses	For accuracy	Synopsis – Statistical Methods Section 9.7.1.6.3
Revised method for assessment of rebound insomnia	Per VHP review; to emphasize assessment of rebound insomnia at individual subject level	Synopsis – Statistical Methods Section 9.7.1.6.3
Provided that for applicable countries, the year of birth will be collected instead of the date of birth	To meet requirements in some countries regarding personally identifying information	Section 9.5.1.1
Specified viral tests for hepatitis B and hepatitis C	To provide additional detail of screening assessments	Section 9.5.1.5.5 Table 4 (footnote “g”)

Revision History: Previous Version (Revised protocol): V2.0 Current Version (Amended protocol): V3.0 Date of Revisions: 24 Jun 2016		
Change	**Rationale**	**Affected Protocol Sections**
Deleted alcohol and nicotine/ cotinine from screening for drugs of abuse	To correct an error, as these drugs are not being tested in the urine drug screen in this study	Section 9.5.1.5.5
Corrected window of study days for Screening	To correct an error	Table 4
Clarified interval for reporting of follow-up SAE, pregnancy, or breastfeeding information	Per VHP review; for accuracy	Section 9.5.4.1
Added sentence distinguishing between definitions of "study completer" per protocol versus for statistical analysis purposes	For clarity	Section 9.5.5
Corrected statement referring to study visit at which randomization occurs	To correct an error	Section 9.5.5
Deleted reference to examples of source documents that will not be used in this study	For accuracy	Section 11.3
Deleted glucose-metabolizing agents from list of prohibited/concomitant medications	This prohibition is considered unnecessary.	Appendix 3
Added Appendix 4 – Prescribing Information for Ambien CR®	For reference	Section 9.4.1 Appendix 4
Revised signature sheet	Changes in corporate structure	Protocol signature page

Revision History: Previous Version (Original protocol): V1.0 Current Version (Revised protocol): V2.0 Date of Revisions: 04 Apr 2016		
Change	**Rationale**	**Affected Protocol Sections**
Specify that an additional secondary objective will be the determination of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL with respect to SE, WASO, TST, sSOL, sSE, sWASO, and sTST at defined time intervals.	The previous description of these comparisons did not make reference to superiority.	Synopsis – Objectives Section 8.2.2
Add an additional secondary objective specifying the evaluation of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL with respect to LPS, separately from comparisons of drug effects on other sleep measures.	Previously, the comparison of LEM5 and LEM10 to ZOL on LPS was not a separate additional secondary objective, and the previous description of these comparisons with regard to LPS did not make reference to superiority.	Synopsis – Objectives Synopsis – Statistical Methods Section 8.2.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Specify that an additional secondary objective will be the evaluation of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL with respect to the proportions of sleep onset and sleep maintenance responders as defined by LPS, WASO, sSOL, and sWASO.	The previous description of these comparisons did not make reference to superiority.	Synopsis – Objectives Section 8.2.2
Specify that an additional secondary objective will be the evaluation of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL and PBO with respect to ISI and FSS	The previous description of these comparisons did not make reference to superiority.	Synopsis – Objectives Section 8.2.2

Revision History: Previous Version (Original protocol): V1.0 Current Version (Revised protocol): V2.0 Date of Revisions: 04 Apr 2016		
Change	**Rationale**	**Affected Protocol Sections**
Add an additional secondary objective specifying the evaluation of whether LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL and PBO with respect to cognitive performance the morning after the first 2 nights of treatment.	Previously, these comparisons were an exploratory objective, and the previous description of these comparisons did not make reference to superiority.	Synopsis – Objectives Section 8.2.2
State as a separate additional secondary endpoint, the change of mean LPS from baseline on Days 1, 2, 29, and 30 of LEM5 and LEM10 compared to ZOL	A separate additional secondary objective was added for the comparison of LEM versus ZOL on LPS. Previously this endpoint for LPS was combined with other sleep variables.	Synopsis—Statistical Methods
Add the descriptor "potential" before cases in the paragraph describing the process to be followed regarding the Cataplexy Adjudication Committee.	For clarity. It is possible that the Cataplexy Adjudication Committee may review cases that are adjudicated as events other than cataplexy, but all potential cases that may be adjudicated as events of cataplexy will be flagged for review.	Section 9.2.5

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	E2006/lemborexant
Indication:	Insomnia
Phase:	3
Approval Date:	V1.0 21 Mar 2016 (original protocol) V2.0 04 Apr 2016 (revised protocol) V3.0 24 Jun 2016 (per Amendment 01) V4.0 16 Jul 2016 (per Amendment 01, editorial corrections) V5.0 16 Feb 2017 (per Amendment 02) V6.0 16 Jun 2017 (per Amendment 03) V7.0 05 Feb 2018 (per Amendment 04)
IND Number:	111,871
EudraCT Number:	2015-004347-39
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder

Investigator(s)

To be determined

Site(s)

Approximately 105 sites in North America and Europe (revised per Amendment 02)

Study Period and Phase of Development

Approximately 64 weeks

Phase 3

Objectives

Primary Objective – US and Non-US (revised per Amendment 03)

- Demonstrate using polysomnography (PSG) that lemborexant (LEM10 and LEM5) is superior to placebo (PBO) on objective sleep onset as assessed by latency to persistent to sleep (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder

Key Secondary Objectives – US ONLY (revised per Amendment 03)

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by sleep efficiency (SE) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by WASO after the last 2 nights of treatment (revised per Amendments 03 and 04)
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to zolpdiem tartrate extended release 6.25 mg (Ambien CR®; ZOL) on wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of treatment

Key Secondary Objectives – Non-US ONLY (revised per Amendment 03)

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by SE after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on wake after sleep onset (WASO) after the last 2 nights of treatment

Additional Secondary Objectives – US and Non-US (revised per Amendment 03)

- Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL on selected PSG variables after the first 2 nights and the last 2 nights of treatment and on selected Sleep Diary variables over the first 7 nights and the last 7 nights of treatment
- Confirm the efficacy of LEM5 and LEM10 compared to placebo (PBO) on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 and determine whether they are superior to that of ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary subjective sleep onset latency (sSOL) and subjective wake after sleep onset (sWASO)
- Evaluate the safety and tolerability of lemborexant
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity

Scale (FSS) at the end of treatment

- Determine whether the safety of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO as assessed by cognitive performance in the morning after the first 2 nights of treatment

Exploratory Objectives – US and Non-US (revised per Amendment 03)

- Explore the effects of LEM5, LEM10, ZOL and PBO on:
  - Subjective quality of sleep
  - Postural stability in the morning after the last 2 nights of treatment
  - Cognitive performance after the last 2 nights of treatment
  - Rebound insomnia in the 2 weeks following 30 days of treatment
  - Subjective ratings of morning sleepiness during and following completion of treatment
  - Sleep architecture parameters and other PSG variables
  - Health outcomes on the Patient Global Impression - Insomnia (PGI-Insomnia) and EQ-5D-3L
  - Withdrawal symptoms after completion of treatment
- Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Conduct population pharmacokinetic (PK) modeling for lemborexant
- Explore PK/pharmacodynamic (PK/PD) relationships between lemborexant concentrations and efficacy and safety variables

Study Design

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males 65 years or older or females 55 years or older. Approximately 60% of the subjects will be age 65 years or older. (revised per Amendment 03)

The study will have 2 phases: The Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights, and a minimum 14-day Follow-up Period before an End of Study (EOS) Visit. (revised per Amendment 02)

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead electrocardiograms (ECGs), vital signs, weight, height, clinical hematology and chemistry analysis and urinalysis, and suicidality.

Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject complains of difficulties with sleep maintenance and/or early morning awakening. Screening assessments will include the ISI, as well as the Epworth Sleepiness Scale (ESS), STOPBang, International Restless Legs Scale (IRLS), and Munich Parasomnia Scale (MUPS), collectively called the Sleep Disorders Screening Battery (SDSB). Other assessments administered will include the FSS and EQ-5D-3L. Additional eligibility criteria will be assessed and safety assessments including the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be conducted. (revised per Amendment 02)

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

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, and provided that the Sleep

Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the second screening visit. (Subjects who are not eligible based on Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day -17 and Day -10. On this and all nights on which PSG is recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test. (revised per Amendment 02)

After check-in has been completed, study personnel will familiarize subjects with the postural stability assessment (Cognitive Drug Research [CDR] posture assessment) and will also conduct a minimum of 2 training sessions for the cognitive performance assessment battery (PAB). 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. Within 5 minutes of morning waketime, the CDR posture and PAB assessments will be administered under the same conditions (eg, timing of assessments relative to waketime, ambient lighting), as will be employed during the testing sessions. The CDR posture and PAB assessments at this time are for familiarization purposes only. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG will be reviewed for exclusion criteria related to symptoms of sleep apnea and/or periodic limb movement disorder. Subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period.

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 subjects will take PBO each night immediately (ie, within 5 minutes) before bedtime (defined as the time the subject intends to try to fall asleep). They will be reminded that they must remain in bed for at least 7 hours each night and maintain a regular bedtime and waketime throughout the study, according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals and use of caffeine and alcohol.

When subjects have completed the Sleep Diary on at least 7 consecutive mornings during the Run-in Period, the diary will be reviewed for continued eligibility with regard to whether the subject continues to report sWASO ≥60 minutes on at least 3 of the 7 nights, as well as the schedule and duration of time spent in bed. Subjects who are still eligible will return to the clinic for the first of 2 consecutive nights on which PSG will be recorded. The first of these 2 nights must be between Day -10 and Day -4. In the evening, before the PSG recording, the ISI, FSS, and EQ-5D-3L will be assessed. The ISI score will be reviewed for eligibility, and safety assessments will be conducted. Study personnel will administer study drug to subjects within 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second screening visit. Subjects will undergo an 8-hour PSG. The next morning, subjects will undergo assessments including the CDR posture and PAB assessments, will complete the Sleep Diary, and will rate their morning sleepiness level at 1.5 hours after waketime. (revised per Amendment 01) The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that is safe for them to do so. (revised per Amendment 02)

Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects within 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will undergo postural stability and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic after the investigator determines that is safe for them to do so.

Subjects will continue to take study drug at home within 5 minutes before bedtime and they will continue to complete the Sleep Diary each morning within 1 hour after morning waketime. 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 Period

After a minimum of 2 nights following the baseline PSGs, the Run-in Period will end and the Baseline Period will take place. On Day 1, subjects will be admitted to the clinic and the ISI, FSS, and EQ-5D-3L will be administered. Blood and urine samples will be collected for routine safety assessments, an ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized, and will begin the Treatment Period. (revised per Amendment 02)

Treatment Period

The Treatment Period will begin on Day 1 and will continue until Day 31. Subjects will be randomized in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO. (revised per Amendment 02)

Within 5 minutes before the subject's MHB, study drug will be administered and an 8-hour overnight PSG will be initiated. At completion of the PSG recording the following morning (Day 2), postural stability will be assessed and the PAB will be conducted immediately thereafter. Subjects will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. (revised per Amendment 01) They may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by an overnight PSG. The next morning (Day 3), CDR posture and PAB assessments will be conducted and a PK sample will be obtained. Subjects will complete the Sleep Diary. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may then leave the clinic after the investigator determines that is safe for them to do so. Study drug will be dispensed and subjects will be provided with instructions to continue completing the Sleep Diary each morning within 1 hour of waketime and taking study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period.

On Day 29, subjects will return to the clinic. Study drug will be administered within 5 minutes before the subject's MHB, followed immediately by a PSG. On the morning of Day 30, CDR posture and PAB assessments will be conducted. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, CDR posture and PAB assessments will be conducted and a PK sample will be obtained. Then the ISI, FSS, EQ-5D-3L and PGI-Insomnia will be administered. Blood and urine samples will be collected for routine safety assessment. An ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Then, after the investigator determines that it is safe for them to do so, subjects will be discharged from the clinic.

Follow-up Period

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

At least 14 days but no more than 18 days after completion of the Treatment Period subjects will return to the clinic for the EOS Visit. The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) and eC-SSRS will be administered, and routine safety assessments will be conducted.

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug, to complete an Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and the AE must be followed to resolution or for 2 weeks, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

Interim Analysis

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately 475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study, which is anticipated to occur by the end of July 2017. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter. (revised per Amendment 03)

Adjudication Committee (revised per Amendment 02)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [SMQ narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia, and transient ischemic attack). To assist in the preparation of narratives about such events and to support the Committee's adjudication process, investigators and site personnel will be instructed to query subjects who report any of the above events for supplemental information about the events, using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events considered serious. (revised per Amendment 02)

End of Study

Estimates for End of Study are as follows:

- The study will begin in approximately April 2016
- The end of the study will be the date of the last study visit for the last subject in the study.

The estimated duration for each subject on study is anticipated to be a maximum of 81 days (11.5 weeks) consisting of the Screening Period plus Run-in Period plus Baseline Period maximum of 35 days plus Treatment Period plus Follow-up Period and EOS Visit maximum of 53 days. A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study. (revised per Amendment 02)

Number of Subjects

Approximately 2800 subjects will be screened to provide approximately 950 randomized subjects. Subjects will be randomized to one of the following treatment arms: LEM5, LEM10, ZOL, or PBO, in an approximate 5:5:5:4 ratio (n=250:250:250:200). Randomization will be stratified by country and age group (55 to 64 years old; 65 years or older). Approximately 60% of the subjects will be age 65 years or older. (revised per Amendments 02 and 03)

Inclusion Criteria

1. Male age 65 years or older or female age 55 years or older at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the subject is not eligible)
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of subjective WASO (sWASO) typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At Screening: Reports habitual bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. At Screening and at check-in before the first PSG during the Run-in Period: ISI score ≥13 (revised per Amendment 02)
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary on the 7 most recent mornings (minimum 5 of 7 for eligibility) before the second screening visit, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that neither bedtime, (defined as the time the subject attempts to try to sleep), nor waketime (defined as the time the subject gets out of bed for the day) deviates more than 1 hour on more than 2 nights from the calculated MHB or median habitual waketime

(MHW), respectively, from the screening Sleep Diary entries

9. 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 second screening visit, such that there are no more than 2 nights with time spent in bed duration < 7 hours or > 10 hours (revised per Amendment 02)
10. During the Run-in Period: Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary on the 7 most recent mornings before the first PSG during the Run-in Period, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
11. During the Run-in Period: Reconfirmation of regular bedtimes and waketimes as defined in Inclusion Criterion 8
12. During the Run-in Period: Reconfirmation of sufficient duration of time spent in bed as defined in Inclusion Criterion 9 (revised per Amendment 02)
13. During the Run-in Period: Objective (PSG) evidence of insomnia as follows: WASO average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes (revised per Amendment 02)
14. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
15. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

Exclusion Criteria

1. 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: (revised per Amendment 01)
    a. STOPBang score ≥5
    b. International Restless Legs Scale score ≥16
    c. Epworth Sleepiness Scale score >15 (Scores of 11-15 require excessive daytime sleepiness to be recorded in subject's Medical History) (revised per Amendments 01 and 02)
2. 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
3. On the MUPS, endorsed the item that corresponds to a history of sleep-eating or reports a history of sleep-related violent behavior, sleep-driving, or symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study (revised per Amendment 02)
4. Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second screening visit
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening
6. Beck Anxiety Index (BAI) score >15 at Screening
7. Habitually naps during the day more than 3 times per week
8. Is a female of childbearing potential

    Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, and are postmenopausal 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).
9. 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
10. History of drug or alcohol dependency or abuse within approximately the previous 2 years
11. 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

12. Known to be positive for human immunodeficiency virus
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
14. A prolonged QT/QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms)
15. Current evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal; 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, including the ability to perform tasks on the cognitive PAB. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. (revised per Amendment 01)
16. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
17. 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, including the ability to perform the PAB.
18. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the eC-SSRS administration during the Prerandomization Phase (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)
19. Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS) (revised per Amendment 02)
20. Scheduled for surgery during the study
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period). (A list of prohibited concomitant medications is presented in Appendix 3 of the protocol) (revised per Amendment 01)
22. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period) (revised per Amendment 01)
23. Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study
25. A positive drug test at Screening, Run-In, or Baseline, or unwilling to refrain from use of recreational drugs during the study
26. Hypersensitivity to lemborexant or zolpidem or to their excipients
27. 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
28. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Test drug

Lemborexant 5 mg or 10 mg, or lemborexant-matched placebo taken orally in tablet form each night for 30 consecutive nights immediately before the time the subject intends to try to sleep

Comparator drug

Zolpidem tartrate extended release 6.25 mg or zolpidem-matched placebo taken orally in tablet form each night for 30 consecutive nights immediately before the time the subject intends to try to sleep

Run-in Period

All subjects will receive 1 lemborexant-matched placebo tablet and 1 zolpidem-matched PBO tablet in a single-blind manner during the Run-in Period

Treatment Period

During the Treatment Period, all subjects will receive 2 tablets as described below according to the treatment arm to which the subject has been randomized:

LEM5: 1 zolpidem-matched placebo tablet and 1 lemborexant 5 mg tablet

LEM10: 1 zolpidem-matched placebo tablet and 1 lemborexant 10 mg tablet

ZOL: 1 zolpidem 6.25 mg tablet and 1 lemborexant-matched placebo tablet

PBO: 1 zolpidem-matched placebo tablet and 1 lemborexant-matched placebo tablet

Duration of Treatment

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

Concomitant Drug/Therapy

Caffeine will be permitted in limited quantities during the study. Subjects will be advised to limit caffeine consumption to ≤4 cups of caffeinated beverages per day, or ≤400 mg caffeine per day. They will be instructed to avoid caffeine after 13:00 on days when they are scheduled for a PSG recording and after 18:00 on all other days during the study.

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcoholic drinks on any day during the study, but will be instructed not to consume any alcohol within 3 hours before bedtime. They must not consume any alcohol on days when they are scheduled for a PSG recording. Compliance with these restrictions will be monitored by specific questions on the Sleep Diary.

Prohibited medications include strong and moderate 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 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 Appendix 3 of the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

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

Assessments

Screening Assessments (administered only at first screening visit)

Sleep Disorders Screening Battery

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
- ESS: a questionnaire that asks the subject to rate their probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, which assesses the severity of daytime sleepiness
- MUPS (adapted version): a scale comprising 21 questions asking whether the subject has experienced

phenomena related to the International Classification of Sleep Disorders Version 2 classified parasomnias (eg, enuresis, sleepwalking, sleep paralysis) along with a time frame for occurrence of these experiences ranging from within past month to lifetime and frequency within the time frame ranging from occasionally to almost every night. (revised per Amendment 01)

Beck Depression Inventory – II

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

Beck Anxiety Inventory

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

Efficacy Assessments

Polysomnography (PSG)

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

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

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

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per time in bed (TIB), calculated as TST/interval from lights off until lights on
- WASO: minutes of wake from the onset of persistent sleep until lights on
- WASO2H: minutes of wake during the interval from 240 minutes after lights off until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least one epoch of wake, after onset of persistent sleep, and including any terminal awakening)

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

- Sleep onset latency: minutes from lights off to the first epoch of any stage of sleep (N1, N2, N3, REM) (revised per Amendment 01)
- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening cannot be interrupted by stage N1, but must be interrupted by stage N2, N3, or REM
- Number of long awakenings
- WASO1H (wake after sleep onset in the first half of the night): minutes of wake during the interval from onset of persistent sleep until 240 minutes after lights off (revised per Amendment 03)
- Percentage of sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and

combined), REM sleep

- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of sleep (N1, N2, N3) to first epoch of REM (revised per Amendment 01)

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

Electronic Sleep Diary

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the study. Sleep Diary entries may be maintained in paper format as a backup to the electronic Sleep Diary, if necessary. This Sleep Diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety. In addition, the Sleep Diary will include questions that relate to morning sleepiness and to alcohol consumption. (revised per Amendment 02)

Sleep parameters:

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

Quality of Sleep:

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

Morning Sleepiness:

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

The morning sleepiness question that is part of the electronic Sleep Diary will also be asked verbatim, using a paper-and-pencil format, at 1.5 hours after waketime each morning the subject is in the clinic following a PSG recording. The rating on this question will be taken into consideration by the investigator when making the determination about whether it is safe for the subject to be discharged from the clinic.

Alcohol Consumption:

The Sleep Diary will include questions to ask whether the subject consumed alcohol the previous day within 3 hours before bedtime, or exceeded the daily maximum of 2 alcoholic drinks, or both. (revised per Amendment 01)

Insomnia Severity Index

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

Fatigue Severity Scale

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS score is the sum of all responses to the 9 questions. Higher scores indicate greater fatigue.

Pharmacokinetic Assessments

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

Pharmacodynamic Assessments

Postural Stability using the CDR Posture Assessment

Postural stability will be assessed using an apparatus similar to the Wright ataxiameter, and referred to as the CDR posture device. The CDR posture device measures directional trunk movements (ie, body sway) through a cord placed around the subject's waist and connected to the ataxiameter. On the evening of the Screening PSG visit, subjects will be introduced to the CDR posture assessment. Subjects will stand on a firm surface with feet comfortably apart, either barefoot or wearing socks. The standing position (inside heel-to-inside heel distance) and barefoot/socks conditions will be documented to ensure they remain the same for a given subject at each postural stability assessment timepoint. They will be instructed to stand as still as possible with eyes closed for 1 minute. (revised per Amendment 01) On the morning after the Screening PSG, subjects will complete a CDR posture assessment session for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, starting within 5 minutes of morning waketime, at bedside) as during the testing sessions at subsequent visits.

Body sway is detected through the cable around the subject's waist by the ataxiameter and these data are transmitted to a laptop. Body sway is measured in units of 1/3° of the angle of arc. For ease in reporting these will be called arbitrary units, with a higher number indicating more body sway (less postural stability).

Cognitive Performance Assessment Battery

A computerized PAB will be administered on a laptop computer after the postural stability test. (revised per Amendment 01) While completing the PAB, subjects will be in bed and ambient lighting will be maintained at a level of 80 – 100 lux at the subject's eye level. On the evening of the Screening PSG visit, before bedtime, subjects will be introduced to the PAB tasks and will undergo a minimum of 2 training sessions. If subjects cannot adequately perform the tasks during the training sessions, they will be excluded from further participation. On the morning after the Screening PSG, subjects will complete a session of the cognitive PAB for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, lighting, subject in bed) as during the testing sessions at subsequent visits.

The PAB comprises 9 tasks including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Numerical Working Memory, Spatial Working Memory, Word Recognition, and Picture Recognition. The full PAB will take approximately 18 to 30 minutes to complete. Four composite domain factor scores are calculated by combining outcome variables from the various tests. The four domain factor scores are Power of Attention, Continuity of Attention, Quality of Memory, and Speed of Memory Retrieval.

- Power of Attention
  - A composite score from the speed scores of 3 tests of attention
  - Reflects the ability to focus attention and process information
- Continuity of Attention
  - A composite score created by combining the accuracy scores from the tests of attention
  - Reflects the ability to sustain attention (vigilance)
- Quality of Memory
  - A composite score created by combining the accuracy measures from the two tests of working memory and the four tests of episodic memory

- Reflects the ability to store information in memory and subsequently retrieve it

- Speed of Memory Retrieval
  - A composite score created by combining the reaction time scores from the two working memory tests and the two episodic recognition tests
  - Reflects time taken to retrieve information held in both working and episodic memory

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, and at the EOS Visit.

Columbia - Suicidality Severity Rating Scale

Suicidality will be assessed using a self-rated electronic version of the C-SSRS (eC-SSRS). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire

An assessment of withdrawal symptoms will be made using the T-BWSQ completed at the EOS Visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes –moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's score. (revised per Amendment 02)

Other Assessments

EQ-5D-3L

The EQ-5D-3L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility. The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

Patient Global Impression – Insomnia

The PGI-Insomnia is a self-report assessment asking about subjects' perceptions of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a) helped/worsened sleep, (b) decreased/increased time to fall asleep, (c) increased/decreased total sleep time, and 1 item related to perceived appropriateness of study medication strength. The first 3 items are answered on a 3-point scale (1=positive medication effect, 2=neutral medication effect, 3=negative medication effect) and the last item on a different 3-point scale (medication: 1=too strong, 2=just right, 3=too weak).

Bioanalytical Methods

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

Statistical Methods

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

Study Endpoints

Primary Endpoint(s)

The primary endpoint is:

- Change from baseline of mean LPS on Days 29 and 30 of LEM10 and LEM5 compared to PBO (revised per Amendment 03)

Secondary Endpoint(s)

Key Secondary Endpoints: US ONLY (revised per Amendment 03)

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO (revised per Amendment 04)

- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 and LEM5 compared to ZOL

Key Secondary Endpoint(s): Non-US ONLY (revised per Amendment 03)

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO

Additional Secondary Endpoints: US and Non-US (revised per Amendment 03)

- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, WASO, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 of LEM5 and LEM10 compared to PBO
- Change from baseline of mean WASO2H and TST on Days 29 and 30 of LEM5 and LEM10 compared to PBO
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO
- Proportion of responders after Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that:
    - Objective sleep onset response is defined as LPS ≤ 20 minutes (provided mean baseline LPS was > 30 minutes)
    - Subjective sleep onset response is defined as sSOL ≤ 20 minutes (provided mean baseline sSOL was > 30 minutes)
    - Objective sleep maintenance response is defined as WASO ≤ 60 minutes (provided mean baseline WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
    - Subjective sleep maintenance response is defined as sWASO ≤ 60 minutes (provided mean WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
- Safety and tolerability of LEM
- Change from baseline of the score from items 4 to 7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

Exploratory Endpoints

The change from baseline of WASO2H for LEM5 and LEM10 compared to ZOL will be considered as exploratory for all non-US submissions. The following endpoints will also be explored for LEM5 and LEM10. Except for PK endpoints, comparisons to ZOL and PBO will be made. (revised per Amendment 03)

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
    - Change from baseline of sSOL at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights(revised per Amendment 03)

  - Change from baseline of sWASO at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7, mean of the second 7 nights (revised per Amendment 03)
  - Proportion of subjects whose sSOL is longer than at Screening at the following timepintgs during the the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean for first 7 nights, mean of the second 7 nights (revised per Amendments 02 and 03)
  - Proportion of subjects whose sWASO is higher than at Screening at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean for the first 7 nights, for thesecond 7 nights (revised per Amendments 02 and 03)
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period
- Change from baseline of mean morning sleepiness ratings assessed at 1.5 hours after waketime when subjects are in clinic on Days 1 and 2, and Days 29 and 30 (revised per Amendment 01)
- Change from baseline of mean minutes and mean percentage (a) per TIB and (b) per TST of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline of mean REM latency, mean number of awakenings, and mean number of long awakenings on Days 1 and 2 and Days 29 and 30 (revised per Amendment 03)
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- Proportion of subjects who score ≥ 3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- PK of lemborexant and its metabolites M4, M9, and M10
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

Analysis Sets

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

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

The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan (SAP).

The PK Analysis Set is the group of subjects who have at least one quantifiable plasma concentration of lemborexant or its metabolites, or zolpidem, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least one quantifiable lemborexant concentration data point as per the PK Analysis Set.

Efficacy Analyses

Definitions of Baseline

Baseline is defined as the means from the 2 PSGs during the Run-in Period for PSG-derived variables and the mean of the last 7 mornings before the first baseline PSG during the Run-in Period for Sleep Diary variables. For other endpoints, baseline data are captured during the Run-in Period and Baseline Period. Details will be specified in the SAP.

Control of Type I Error (revised per Amendment 03)

A sequential gate-keeping procedure will be used for the primary and the key secondary endpoint comparisons to control for the overall type I error at the 0.05 significance level. The first endpoint comparison will be tested

at the 0.05 significance level. If the testing is found to be statistically significant, then proceed to the next endpoint testing at significance level of 0.05, otherwise stop testing.

The primary endpoints will be tested in the following order:

- Change from baseline of the mean LPS of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean LPS of Days 29 and 30 of LEM5 compared to PBO

The key secondary endpoints will only be tested if both primary analyses are statistically significant at the 0.05 level. The key secondary endpoints will be tested in the following order:

US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO (revised per Amendment 04)
- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO (revised per Amendment 04)
- Change from baseline of the mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL

Non-US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO

No multiplicity adjustment will be done on other efficacy analyses.

Analysis for the Primary Endpoint

Null Hypothesis: No difference exists in the mean change from baseline of the mean LPS of Days 29 and 30 for treatment with LEM10 (or LEM5) as compared with PBO. (revised per Amendment 03)

Alternative Hypothesis: A difference exists in the mean change from baseline of the mean LPS of Days 29 and 30 for LEM10 (or LEM5) compared to PBO. (revised per Amendment 03)

The LPS change from baseline (the mean of Days 1 and 2, and the mean of Days 29 and 30) will be analyzed using the mixed effect model repeated measurement analysis (MMRM) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), region, age group (55 – <65 years; 65 years or older), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time (revised per Amendment 04). Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputations (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed primary efficacy assessments without missing values) (revised per Amendment 04). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided. (revised per Amendment 03)

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

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described above will be repeated on subjects who completed all efficacy assessments and have no missing values.
- As-treated analysis: The same primary efficacy analyses (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.

- MMRM analysis assuming missing at random (MAR): The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are MAR.
- MI Imputation assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows): (revised per Amendment 04)

Study days where results are available	1	2	29	30
Pattern 1	x	x	x	x
Pattern 2	x	x	x	.
Pattern 3	x	x	.	.
Pattern 4	x	.	.	.
x = result present; . = result missing				

- Tipping point analysis: A range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant. (revised per Amendment 04)

Secondary Efficacy Analyses

Key Secondary Efficacy Analysis (revised per Amendments 03 and 04)

Changes from baseline of mean SE, WASO2H, and WASO of Days 1 and 2 and the mean of Days 29 and 30 will be analyzed using a pattern mixture model utilizing MI assuming MNAR. The treatment comparison will be performed using contrasts. The p-value, LS means and the 95% CI of the treatment differences will also be provided. The comparison of LEM10 and LEM5 to ZOL on WASO2H will be considered as exploratory for all non-US submissions. (revised per Amendment 03)

Other Secondary Efficacy Analyses (revised per Amendment 03)

The other secondary efficacy endpoints (change from baseline of the mean of the following endpoints: LPS, SE, WASO2H, and WASO of the mean of Days 1 and 2; TST of the mean of Days 1 and 2 and of the mean of Days 29 and 30; sSOL, sWASO, sSE, and sTST for the mean of the first 7 and last 7 days of the Treatment Period) will be analyzed using MMRM assuming MAR. (revised per Amendment 03)

The proportion of responders will be analyzed using the Cochran-Mantel-Haenszel test, controlled for region and age group, for each dose of lemborexant compared to PBO and ZOL. The analysis will be similarly repeated for responder analysis based on Sleep Diary variables (sSOL and sWASO) over the first 7 and last 7 nights of treatment. (revised per Amendment 03)

The change from baseline of the ISI total of four items on daytime functioning at Day 31 and the FSS score at Day 31 will be analyzed using analysis of covariance (ANCOVA), adjusted for the corresponding baseline value, age group, region, and treatment. (revised per Amendment 03)

Changes from baseline in mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval for the PAB tasks will be analyzed using MMRM assuming MAR. (revised per Amendments 01 and 03)

Secondary endpoints may also be presented graphically or analyzed by modeling methods if warranted. (revised per Amendment 03)

No multiplicity adjustment or missing values imputation is planned for other secondary analyses. (revised per Amendment 03)

Exploratory and Pharmacodynamic Analyses

The change from baseline mean score of the quality of sleep item on the Sleep Diary for the means of the first 7 days and last 7 days of the Treatment Period will be analyzed using MMRM assuming MAR. (revised per Amendment 03)

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep Diary data from the Follow-up Period will be compared to Sleep Diary data from the Screening Period to assess whether subjects experience rebound insomnia. Specifically, a higher value for sSOL or sWASO during

the Follow-up Period compared to the mean sSOL or sWASO value during the Screening Period will be considered worsened sleep. (revised per Amendment 02)

To assess rebound insomnia, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the first 3 nights, the mean of the first 3 nights, and the mean of each of the 2 weeks of the Follow-up Period the proportion of subjects whose corresponding value for sSOL or sWASO exceeds the corresponding Screening Period value by 5 minutes will be summarized by treatment group and compared to placebo. The percentage of 'rebounders' between each treatment and placebo group will be analyzed using a CMH test. (revised per Amendments 01, 02, and 03)

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for region, age group and treatment. The LS mean of each of the first 3 nights and each week of the Follow-up Period will be compared to the Screening Period between each treatment group and placebo. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. (revised per Amendments 01 and 03)

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-up Period will be analyzed using MMRM assuming MAR. Change from baseline of the mean morning sleepiness ratings assessed at 1.5 hours after waketime when subjects are in clinic on days 1 and 2 and days 29 and 30 will be similarly analyzed using MMRM assuming MAR. (revised per Amendments 01 and 03)

The change from baseline of the mean of Days 1 and 2 and of the mean of Days 29 and 30 for the sleep architecture and other PSG endpoints (WASO1H minutes and percentage [a] per TIB and [b] per TST of sleep stage N1, N2, N3, total NREM and REM; REM latency, DurLongAW, number of awakenings, number of long awakenings, REM episode frequency and duration, and mean REM/NREM cycle duration) will be summarized. (revised per Amendment 03)

Each item on the PGI-Insomnia at Day 31 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

The change from baseline in the EQ-5D-3L score at Day 31 will be analyzed using ANCOVA, adjusted for region, age group and treatment. (revised per Amendment 03)

No multiplicity adjustment or missing value imputation is planned for exploratory and pharmocodynamic analyses. (revised per Amendment 03)

Pharmacokinetic Analysis

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

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK analysis data from this study will be pooled with relevant data from Phase 1 and 2 studies, and other Phase 3 studies if available. The effect of covariates (ie, demographics) on the PK of lemborexant will be evaluated. The PK model will be parameterized for apparent total clearance following extravascular administration (CL/F) and volumes of distribution. Derived exposure parameters such as area under the concentration-time curve (AUC), maximum lemborexant plasma concentration (C_{max}) and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL/F and dosing history.

Pharmacodynamic Analysis

These analyses are described in the Secondary Efficacy Analyses, and Exploratory and Pharmacodynamic Analyses sections (above).

Pharmacokinetic/Pharmacodynamic Analysis

The PK/PD relationship between exposure to lemborexant and efficacy variables including but not limited to

LPS and WASO, and safety variables including but not limited to morning sleepiness and frequently occurring treatment-emergent adverse events (TEAEs), will be explored graphically. Any emergent PK/PD relationships will be evaluated by population PK/PD modeling. The population PK/PD analysis plan will be described and results will be reported in a separate document.

Population PK and PK/PD analyses will be performed using NONMEM version 7.2 or later.

Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs and weight, suicidality (eC-SSRS), and T-BWSQ (including frequency and percentage of subjects with T-BWSQ score ≥3), along with change from baseline in laboratory safety test variables, ECGs, and vital sign and weight measurements, will be summarized by treatment group using descriptive statistics.

Other Analyses

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

Although ZOL is included in the study as an active comparator, comparison of ZOL to PBO, and comparison between LEM10 and LEM5 may be made to facilitate evaluation of study results.

Interim Analyses

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the conditional power will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved with the conduct of the study will have access to the interim data or the results of the interim analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis was concluded.

Sample Size Rationale

The sample size was estimated for each comparison of LEM10 vs. PBO, and LEM5 vs PBO with respect to the mean change from baseline of LPS at Month 1, on the basis of a 2-sided t-test at the 0.05 α-level for each treatment comparison. (revised per Amendment 03)

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the standard deviation (SD) of change from baseline for log-transformed LPS is assumed to be 0.9. The LS mean treatment difference at Days 14/15 from Study 201 for log-transformed LPS of LEM10 and LEM5 compared with PBO was 0.75 and -1.15, respectively. Therefore, a sample size of 250 subjects for LEM5, 250 subjects for LEM10, and 200 subjects for PBO has at least 95% power for each treatment comparison, LEM10 with PBO, and LEM5 with PBO, based on 2-sided, 2-sample t-test at 5% significance level. (revised per Amendment 03)

Power is also estimated for the key secondary objectives, the comparison of LEM10 and LEM5 to PBO on

change from baseline of SE and WASO, and LEM10 and LEM5 to ZOL on WASO2H. A sample size of 250 subjects each for LEM5, LEM10, and ZOL, and 200 subjects for PBO has at least 95% power for detecting a statistically significant difference between LEM and PBO for change from baseline in SE, at least 80% power for detecting a statistically significant difference between LEM10 and ZOL/PBO for change from baseline in WASO/WASO2H based on 2-sided 2-sample t-test at 5% significance level. (revised per Amendments 03 and 04)

Endpoint (Test)	Estimated Treatment Difference	Estimated SD	Power
Log(LPS) (LEM5 vs PBO)	-0.75	0.9	>95%
Log(LPS) (LEM10 vs PBO)	-1.15	0.9	>95%
SE (LEM5 vs PBO)	5%	14%	>95%
SE (LEM10 vs PBO)	7%	14%	>95%
WASO (LEM5 vs PBO)	-10 min	55 min	48%
WASO (LEM10 vs PBO)	-15 min	55 min	81%
WASO2H (LEM5 vs ZOL)	-8 min	38 min	65%
WASO2H (LEM10 vs ZOL)	-11 min	38 min	89%

Estimated treatment difference and SD are based on Study 201.

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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
CDR	Cognitive Drug Research
CFR	Code of Federal Regulations
CI	confidence interval
CL	total clearance
CL/F	apparent total clearance following extravascular administration
CPAP	continuous positive airway pressure (revised per Amendment 01)
C_{max}	maximum observed concentration
CPMP	Committee for Proprietary Medicinal Products,
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
DORA	dual orexin receptor antagonist
EASS	events associated with special situations
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EEG	electroencephalogram
EMG	electromyography
EOS	end of study
ESS	Epworth Sleepiness Scale
ET	early termination
EU	European Union
FAS	Full Analysis Set

Abbreviation	Term
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IR	immediate release
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
IxRS	an interactive voice and web response system
KSS	Karolinska Sleepiness Scale
LDA	longitudinal data analysis
LEM5	lemborexant, 5-mg dose
LEM10	lemborexant, 10-mg dose
LNH	low-normal-high
LPS	latency to persistent sleep
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MHB	median habitual sleep time
MI	multiple imputations
M-MSLT	modified multiple sleep onset latency test
MNAR	missing not at random
MUPS	Munich Parasomnia Scale
NREM	non-REM sleep
PAB	performance assessment battery
PBO	placebo
PD	pharmacodynamic(s)
PGI	Patient Global Impression
PI	principal investigator
PK	pharmacokinetic(s)
PSG	polysomnography
PT	preferred term
QTcF	QT interval corrected for heart rate by Fridericia's formula

Abbreviation	Term
RBC	red blood cells
REM	rapid eye movement (sleep stage)
SAE	serious adverse event
SAP	statistical analysis plan
SDSB	Sleep Disorders Screening Battery
SE	sleep efficiency
SOC	system organ class
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
T-BWSQ	Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
TEAE	treatment-emergent adverse event
TIB	time in bed
TST	total sleep time
US	United States
WASO	wake after sleep onset
WASO1H	wake after sleep onset in the first half of the night
WASO2H	wake after sleep onset in the second half of the night
WBC	white blood cells
ZOL	zolpidem tartrate extended release 6.25 mg (Ambien CR®)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- 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. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. 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 105 investigational sites in North America and Europe. (revised per Amendment 02)

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 provided to each site.

7 INTRODUCTION

7.1 Indication

7.1.1 Current Therapeutic Options

Insomnia is a sleep disorder characterized by difficulties with sleep onset, sleep maintenance, or early morning awakening, in association with a complaint of impairment during the daytime. Insomnia is a widespread problem in industrialized nations, with approximately 30% of the population having symptoms and at least 6% meeting diagnostic criteria for insomnia meriting treatment. Currently available pharmacological treatments used for insomnia include benzodiazepines, non-benzodiazepine γ-aminobutyric acid (GABA) receptor agonists (GABAergics), a recently approved dual orexin receptor antagonist (DORA), sedating antidepressants, melatonin and melatonin agonists, antihistamines, and other prescription and non-prescription medications with sedative properties.

The current commercial environment is generic, with the non-benzodiazepine, zolpidem (Ambien®), leading in prescriptions in the US. Other so-called "z-drugs" including zaleplon and eszopiclone, contribute substantially to market share as well. However, there are efficacy and safety concerns associated with the use of z-drugs, particularly zolpidem, particularly in older patients. This limited efficacy is characteristic of short-acting non-benzodiazepine hypnotics and represents an important unmet medical need, as sleep maintenance insomnia is the most prevalent type of insomnia experienced in aging. Up to 50% of individuals over age 55 report difficulty maintaining sleep. The recently approved DORA, suvorexant, was shown in clinical trials to significantly improve sleep maintenance insomnia, but at the starting dose approved for use, showed suboptimal efficacy.

7.1.2 Lemborexant (E2006)

7.1.2.1 Mechanism of Action

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

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

7.1.2.2 Clinical Experience with Lemborexant

7.1.2.2.1 PHASE 1

E2006-A001-001 (Study 001): single ascending dose study. This study included healthy subjects and otherwise healthy subjects with primary insomnia. In addition to determining

the safety and tolerability of single doses, the study provided preliminary evidence of efficacy in the target patient population.

E2006-A001-002 (Study 002): multiple ascending dose study. This study enrolled healthy adult and elderly subjects, each of whom was dosed with lemborexant or placebo 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 CYP3A lead to higher plasma concentrations of lemborexant; and (2) strong inducers of CYP3A lead to notably lower plasma concentrations of lemborexant. The study also demonstrated a weak effect of lemborexant on CYP2B6 activity and no effect on CYP3A activity.

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

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

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

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

in average time to sleep onset in the morning hours, supporting the safety of these doses and their use in Phase 3 studies.

7.1.2.2.2 PHASE 2

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

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

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

Overall, data from the clinical program to date have shown an acceptable safety and tolerability profile of lemborexant, and efficacy on both objective and subjective measures of sleep onset and sleep maintenance.

7.2 Study Rationale

The purpose of this study is to provide important information to begin to improve on the current treatment paradigm for older patients with sleep maintenance insomnia. The study will help establish the efficacy of lemborexant for the treatment of sleep onset and sleep maintenance difficulties, by comparing change from baseline in these parameters to placebo. With respect to comparisons to existing therapies, the current market leader, zolpidem has been shown to improve sleep onset insomnia. The immediate release (IR) formulation of zolpidem is not, however, indicated for sleep-maintenance insomnia. The extended release formulation, zolpidem tartrate extended release 6.25 mg (Ambien CR®; ZOL), was approved by the Food and Drug Administration (FDA) for the treatment of sleep maintenance symptoms as well as for sleep onset difficulties. However, 2 studies, one using 12.5 mg in adults and the other studying 6.25 mg in elderly patients, reported that effects on WASO after nights 1 and 2 of treatment were only statistically significantly different from placebo

for the first 6 hours (adults) or first 5 hours (elderly) of the 8-hour sleep period. After 2 weeks of treatment, WASO was significantly decreased for only the first 5 hours (adults) and first 4 hours (elderly) of the 8-hour sleep period. Given that this is the time of night when most sleep maintenance difficulties are experienced, particularly by elderly individuals, there is an unmet need that has not been effectively addressed with ZOL. In brief, while ZOL improves sleep maintenance more than the IR formulation, it does not sufficiently decrease WASO in the second half of the night (WASO2H). Nonetheless, ZOL was approved based on data for the first 6 hours of the sleep period. It should be noted that the pivotal studies for ZOL were based on data from 3-week trials analyzed for Nights 1/2 and 15/16. A comparison of lemborexant with ZOL, especially with respect to sleep maintenance, would provide clinically meaningful information for clinicians and patients. (revised per Amendment 03)

8 STUDY OBJECTIVES

8.1 Primary Objective – US and Non-US (revised per Amendment 03)

Demonstrate using PSG that lemborexant (LEM10 and LEM5) is superior to PBO on objective sleep onset as assessed by LPS after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

8.2 Secondary Objectives

8.2.1 Key Secondary Objectives – US ONLY (revised per Amendment 03)

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by sleep efficiency (SE) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10) and LEM5) is superior to PBO on sleep maintenance as assessed by WASO after the last 2 nights of treatment (revised per Amendment 04)
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to ZOL on WASO2H after the last 2 nights of treatment

8.2.2 Key Secondary Objectives – Non-US ONLY (revised per Amendment 03)

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by SE after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) are superior to PBO on WASO after the last 2 nights of treatment

8.2.3 Additional Secondary Objectives – US and Non-US (revised per Amendment 03)

- Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment
- Determine whether the efficacy of LEM5 or LEM10, or both LEM5 and LEM10, is superior to that of ZOL on selected PSG variables after the first 2 nights and the last 2 nights of treatment and on selected Sleep Diary variables over the first 7 nights and last 7 nights of treatment.
- Confirm the efficacy of LEM5 and LEM10 compared to PBO on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 and determine whether they are superior to those for ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary subjective sleep onset latency (sSOL) and subjective wake after sleep onset (sWASO)
- Evaluate the safety and tolerability of lemborexant

- Determine whether the efficacy of LEM5 or LEM10, or both LEM5 and LEM10, is superior to that of ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) at the end of treatment
- Determine whether the safety of LEM5 or LEM10, or both LEM5 and LEM10, is superior to that of ZOL and PBO as assessed by cognitive performance in the morning after the first 2 nights of treatment

8.3 Exploratory Objectives – US and Non-US (revised per Amendment 03)

- Explore the effects of LEM5, LEM10, ZOL and PBO on:
  - Subjective quality of sleep
  - Postural stability in the morning after the last 2 nights of treatment
  - Cognitive performance after the last 2 nights of treatment
  - Rebound insomnia in the 2 weeks following 30 days of treatment
  - Subjective ratings of morning sleepiness during and following completion of treatment
  - Sleep architecture parameters and other PSG variables
  - Health outcomes on the Patient Global Impression - Insomnia (Patient Global Impression [PGI]-Insomnia) and EQ-5D-3L
  - Withdrawal symptoms after completion of treatment
- Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Conduct population PK modeling for lemborexant
- Explore PK/PD relationships between lemborexant concentrations and efficacy and safety variables

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ie, ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males 65 years or older or females 55 years or older. Approximately 60% of the population will be age 65 years or older. (revised per Amendment 03)

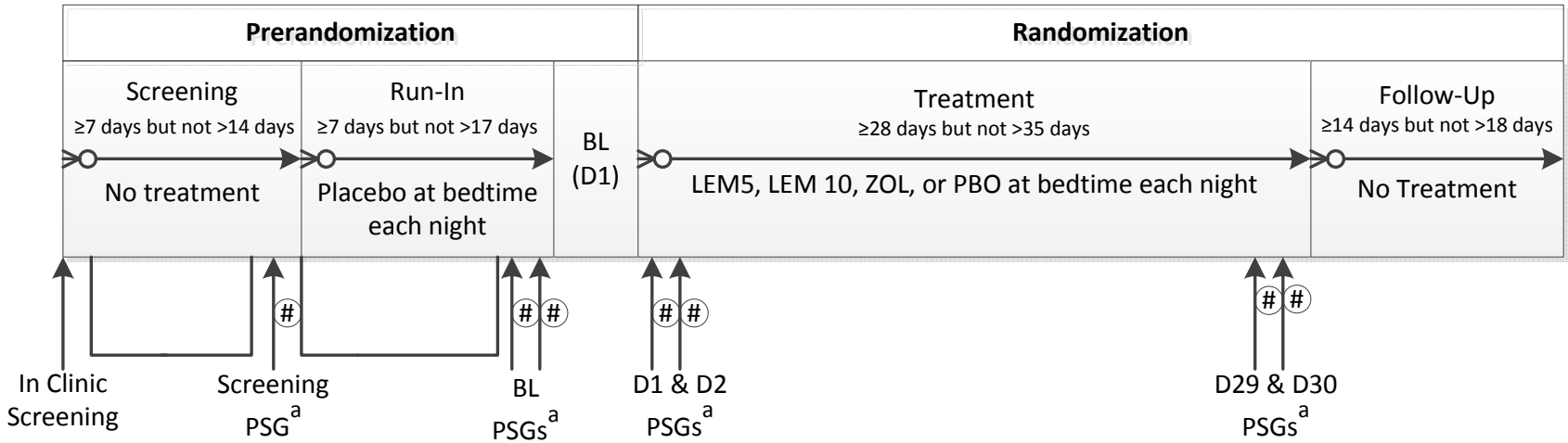
The study will have 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights followed by a minimum 14-day interval before an End of Study (EOS) Visit. (revised per Amendment 02)

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding AEs, 12-lead electrocardiograms (ECGs), vital signs, weight, height, clinical hematology and chemistry analysis and urinalysis, and suicidality.

Estimates for End of study are as follows:

- The study will begin in approximately Apr 2016
- The end of the study will be the date of the last study visit for the last subject in the study.
- The estimated duration for each subject on study is anticipated to be a maximum of 81 days / 11.5 weeks (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 53 days). A subject who completes the Treatment Period (assessments through discharge from clinic on the morning of Day 31) will be considered to have completed the study. (revised per Amendment 02)

The study design is shown in Figure 1.



= CDR Posture and cognitive PAB assessments in the morning following the PSG assessment.
a: All PSG visits will require an overnight stay in the clinic. At least 2 nights must intervene between the second BL PSG and BL (D1).

Figure 1 Schematic Diagram of E2006-G000-304 Study Design

"D" refers to the study day.

BL = baseline, CDR = Cognitive Drug Research, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PAB = performance assessment battery, PBO = placebo, PSG = polysomnography, ZOL = zolpidem tartrate extended release 6.25 mg.

9.1.1 Prerandomization Phase

9.1.1.1 Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the first screening visit (Visit 1), informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject complains of difficulties with sleep maintenance or early morning awakening, or both. Screening assessments will include the ISI, as well as the Epworth Sleepiness Scale (ESS), the STOPBang, the International Restless Legs Scale (IRLS), and the Munich Parasomnia Scale (MUPS), collectively called the Sleep Disorders Screening Battery (SDSB). Additional eligibility criteria will be assessed and safety assessments will be conducted as described in Section 9.5.1.5 and summarized in Table 4. (revised per Amendment 02)

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

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, and provided that the Sleep Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the second screening visit. (Subjects who are not eligible on the basis of Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) This visit must occur between Day -17 and Day -10. On this and all nights on which PSG is to be recorded, subjects will arrive at the clinic in the evening with sufficient time before bedtime to complete check-in procedures, any scheduled assessments, and preparations (eg, electrode montage placement) for the PSG recordings. In addition, at check-in before all visits at which PSG is to be recorded, subjects will undergo a urine drug test. (revised per Amendment 02)

After check-in has been completed, study personnel will familiarize subjects with the postural stability assessment (CDR posture assessment) and will also conduct a minimum of 2 training sessions for the cognitive performance assessment battery (PAB). 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. Within 5 minutes of morning waketime, the CDR posture and PAB assessments will be administered under the same conditions (eg, timing of assessments relative to waketime, ambient lighting), as will be employed during the testing sessions. The CDR

posture and PAB assessments at this time are for familiarization purposes only. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG will be reviewed for exclusion criteria related to absence of symptoms of sleep apnea and/or periodic limb movement disorder, subjects who continue to meet the eligibility criteria will then be dispensed PBO tablets (single-blind) and will enter the Run-in Period.

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, subjects will take PBO each night immediately (ie, within 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 throughout the study according to the schedule determined by the study site and the subject. They will also be reminded that they must follow study restrictions with regard to timing of meals and use of caffeine and alcohol.

When subjects have completed the Sleep Diary on at least 7 consecutive mornings during the Run-In Period, the diary will be reviewed for continued eligibility with regard to whether the subject continues to report sWASO ≥60 minutes on at least 3 of the 7 nights, as well as the schedule and duration of time spent in bed. Subjects who are still eligible will return to the clinic for the first of two consecutive nights on which PSG will be recorded. (Subjects who are not eligible on the basis of Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment.) The first of these 2 nights must be between Day -10 and Day -4. In the evening before the PSG recording, the ISI, the FSS, and the EQ-5D-3L will be assessed. The ISI score will be reviewed for eligibility and safety assessments will be conducted. Study personnel will administer study drug to subjects within 5 minutes before their scheduled bedtime, which will be at the same MHB as used for the second screening visit. Subjects will then undergo an 8-hour PSG. The next morning, subjects will undergo assessments including the CDR posture and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility and subjects may then leave the clinic only after the investigator determines that is safe for them to do so. (revised per Amendment 02)

Subjects will return to the clinic that evening. Study personnel will administer study drug to subjects within 5 minutes before the scheduled bedtime. A PSG will be recorded overnight. The following morning subjects will undergo postural stability and PAB assessments and will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. The PSG recording will be reviewed for continued eligibility, and both PSGs during the Run-in Period will also serve as the baseline for PSG-derived endpoints for subjects who are randomized. Subjects may then leave the clinic only after the investigator determines that is safe for them to do so.

Subjects will continue to take study drug at home within 5 minutes before bedtime and they will continue to complete the Sleep Diary each morning within 1 hour after morning waketime. 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

After a minimum of 2 nights following the baseline PSGs, the Run-in Period will end and the Baseline Period will take place. On Day 1 subjects will be admitted to the clinic and the ISI, FSS, and EQ-5D-3L will be administered. Blood and urine samples will be collected for routine safety assessments, ECG will be performed, and vital signs and weight will be assessed. The electronic Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized and will begin the Treatment Period. (revised per Amendment 02)

9.1.2 Randomization Phase

9.1.2.1 Treatment Period

The Treatment Period will begin on Day 1, and will continue until Day 31. Subjects will be randomized in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO. (revised per Amendment 02)

Within 5 minutes before the subject's MHB, study drug will be administered and an overnight PSG will be initiated. At completion of the PSG recording the following morning (Day 2), postural stability will be assessed and the PAB will be conducted immediately thereafter. Subjects will complete the Sleep Diary. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. (revised per Amendment 01) They may then leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 2, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by an overnight PSG. The next morning (Day 3), the CDR posture and PAB assessments will be conducted and a PK blood sample will be obtained.

Subjects will complete the Sleep Diary. The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may then leave the clinic after the investigator determines that is safe for them to do so. Study drug will be dispensed, and subjects will be provided with instructions to continue to complete the Sleep Diary each morning within 1 hour of waketime and to take study drug daily at home according to the same schedule and with the same instructions as during the Run-in Period.

On Day 29, subjects will return to the clinic. Study drug will be administered within 5 minutes before the subject's MHB, followed immediately by a PSG. On the morning of Day 30, postural stability will be assessed and the PAB will be conducted. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Subjects may leave the clinic after the investigator determines that is safe for them to do so.

On the evening of Day 30, subjects will return to the clinic. A PK blood sample will be collected predose and study drug will be administered within 5 minutes before the subject's MHB, followed by a PSG. On the morning of Day 31, postural stability and PAB assessments will be conducted and a PK sample will be obtained. Then the ISI, FSS, EQ-5D-3L and PGI-Insomnia will be administered. Blood and urine samples will be collected for routine safety assessment. An ECG will be performed, and vital signs and weight will be assessed. The eC-SSRS will be administered. At 1.5 hours after waketime, subjects will rate their morning sleepiness level. Then, 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

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

At least 14 days but no more than 18 days after completion of the Treatment Period, subjects will return to the clinic for the EOS Visit. The Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) and eC-SSRS will be administered, and routine safety assessments will be conducted.

A subject who prematurely discontinues taking study drug should return to the clinic as soon as practicable after discontinuing study drug, to complete an Early Termination (ET) Visit. If the subject discontinues from the study due to an AE, the subject must complete an ET Visit and the AE must be followed to resolution or for 2 weeks, whichever comes first. In addition, subjects who withdraw due to an AE should undergo a urine drug test.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Randomization

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

9.2.2 Run-In

Insomnia trials are associated with large placebo effects. This study will include a placebo Run-in Period to exclude subjects who show a response to placebo. (revised per Amendment 03)

The Run-in Period will also help to identify and exclude subjects who are not compliant with the Sleep Diary instructions, duration of time spent in bed, or restrictions on alcohol use. In this regard, it is necessary for the subjects to be taking PBO and to obtain Sleep Diary data for a minimum of 1 week to adequately evaluate whether there is a PBO response and

compliance with the alcohol-related study restrictions. After this minimum 7 nights of treatment, eligible subjects will have PSG recordings on 2 consecutive nights. These recordings will be used to further screen for eligibility, and will serve as baseline values for those subjects who continue to randomization.

9.2.3 Efficacy Assessments

The study uses objective (PSG) as well as subjective (Sleep Diary) assessments of efficacy. Both assessments have been widely used in registration trials evaluating treatments for insomnia disorder. While PSG indicates that a measurable physiological effect of the study drug has occurred, Sleep Diary outcomes indicate the magnitude of the effect for the patient. (revised per Amendment 03)

Another focus of this study is on WASO2H, a measure of sleep maintenance in the second half of the night. The rationale for the selection of this endpoint is based on the loss of effect of ZOL on sleep maintenance at the end of the sleep period. However, any benefit on WASO2H observed with lemborexant must not be due to a worsening of sleep latency or continuity at the beginning of the night. Therefore, analyses of both LPS and total WASO as well as other PSG variables (eg, total sleep time [TST], number and duration of awakenings) will be conducted to confirm the efficacy of lemborexant on sleep onset and sleep maintenance. (revised per Amendment 03)

9.2.4 Morning Residual Effects on Postural Stability and Cognitive Performance

Non-benzodiazepine sleep-inducing agents such as zolpidem have been associated with motor and cognitive impairment, and laboratory studies have evaluated these impairments both during the middle of the night several hours postdose, and in the morning hours shortly after awakening. Of clinical importance is that the elderly are particularly sensitive to effects of zolpidem on postural stability, which is especially problematic given the increased risk of falls in the elderly.

Moderate to large treatment effects versus placebo on measures of postural stability and cognitive performance have been reported for both 5 mg and 10 mg doses of the IR formulation of zolpidem (Allain, et al., 2003, Mets, et al., 2010, and Boyle, et al., 2009; reviewed in Stranks and Crowe, 2014). Larger impairments are observed near the C_{max} of the zolpidem IR formulation at approximately 1.5 hours postdose than at later timepoints relative to dosing, but there remains a moderate impairing effect of zolpidem even the next morning on certain cognitive domains including attention and memory (Stranks and Crowe, 2014).

With regard to postural stability as measured in this study, zolpidem is assumed to have the same effect on body sway as alcohol at 4.5 hours after dosing (Wesnes, et al., 2000). Further, there is consistent evidence that the effects on postural stability of hypnotic drugs are larger after the first one or two nights of dosing and dissipate thereafter, which has been explained as due to behavioral tolerance (Mets, et al., 2010). For this reason, the key secondary objective for the current study is to compare the effects of lemborexant to those of zolpidem on postural stability at the beginning of treatment, in the morning shortly after waketime on Day 2 and Day 3. Whether there are differential effects of lemborexant and

zolpidem on postural stability at the end of treatment (Day 30 and Day 31) will be explored. Effects on cognitive performance in the morning shortly after waketime will be exploratory for both the beginning and end of treatment.

9.2.5 Adjudication Committee (revised per Amendment 02)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions, atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information about events of cataplexy or potential cataplexy events, using a questionnaire for events potential related to cataplexy and the SAE form for any of the above events considered serious. (revised per Amendment 02)

9.2.6 Study Duration

The registration trials for zolpidem were 3 weeks in duration, with analyses of PSG efficacy data conducted after the first 2 doses and at the end of 2 weeks of active treatment. As noted, treatment benefit of zolpidem declined over time such that WASO2H, particularly in the last 2 hours of the night, was not different from placebo on Nights 15/16 in the zolpidem registration trials. In contrast, when lemborexant was studied for 15 nights of treatment in Study 201, the treatment benefit was maintained such that there was no significant difference in LPS, WASO, or WASO2H between the first 2 and last 2 nights of treatment. Study 304 includes 30 days of active treatment. Based on the results of Study 201, it is expected that there will not be a loss of efficacy of lemborexant between 2 weeks and 4 weeks of treatment.

Moreover, as the beneficial effects of zolpidem on WASO2H did not persist for 2 weeks, it is not expected that there will be statistically or clinically significant effects of ZOL at the end of the 30 days of treatment.

9.2.7 Age Group

While the lower age is not the typical 65 years defining "elderly," it is physiologically meaningful, as insomnia incidence increases at middle age in both men and women, with a particularly steep increase in incidence in women at menopause. In addition, the homeostatic and circadian regulation of sleep are disturbed in many older individuals, which manifests most frequently as sleep maintenance insomnia in the second half of the night, and early morning awakening. The preponderance of sleep maintenance issues in the second half of the sleep period is clear from the literature as well as supported by analyses of data by age group from Study 201. (revised per Amendment 03)

When Study 201 data were analyzed separately for those aged 55 years and older, the apparent treatment effect of lemborexant versus placebo on WASO2H, as well as on WASO, was larger than for the full sample (all ages studied), suggesting that older individuals may be most likely to benefit from a treatment that reduced difficulties with both sleep onset and sleep maintenance. Table 1 shows the least square (LS) mean treatment difference between lemborexant and PBO for various dose groups and dose group combinations from Study 201 for the full sample and for those aged 55 and older. Caution must be exercised concerning the predictive ability of these data, however, since the observed variability in WASO2H was larger in the older subjects. For this reason, a conservative estimate of the expected treatment difference between lemborexant and PBO for WASO2H at the end of treatment was used for power analyses and sample size justification. Enrollment in this study is exclusively older subjects, aged 55 years and older. (revised per Amendment 03)

Table 1 Treatment Effect for Lemborexant versus Placebo (Study 201)

	Treatment Effect in Minutes (95% CI)		
	5 mg	**10 mg**	**5 and 10 mg combined**
Entire Subject Sample	-7.97 (-19.2, 3.23)	-11.8 (-23.6, -0.05)	-10.0 (-20.6, 0.55)
Aged 55 and Older	-23.9 (-43.8, -3.95)	-14.8 (-36.9, 7.36)	-20.2 (-40.1, -0.35)

CI = confidence interval

9.2.8 Time of Dosing

The time of dosing of study drug will be within 5 minutes before bedtime on nights in the clinic. On nights at home, subjects will be instructed to take study drug just before they intend to try to fall asleep, but as consistently as possible with respect to the time across the study.

9.2.9 Interim Analysis

An interim analysis is planned to be conducted after 50% of the subjects (approximately 475 subjects) have been randomized and have either completed Day 31 assessments or discontinued from the study. The purpose of this analysis is to determine the conditional probability that a statistically significant difference between LEM10 and ZOL on WASO2H will emerge at the end of treatment. This interim analysis will be conducted by an independent statistician external to the Sponsor. The role of the independent statistician and procedures undertaken to preclude potential bias will be detailed in the statistical analysis plan (SAP) and in the Charter.

9.3 Selection of Study Population

Approximately 2800 subjects will be screened and approximately 950 subjects will be randomized at approximately 105 sites in North America and Europe. 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. (revised per Amendment 02)

9.3.1 Inclusion Criteria

1. Male age 65 years or older or female, age 55 years or older at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the subject is not eligible)
   - Frequency of complaint ≥ 3 times per week
   - Duration of complaint ≥ 3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of subjective WASO (sWASO) typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At Screening: Reports habitual bedtime, defined as the time the subject attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. At Screening and at check-in before the first PSG during the Run-in Period: ISI score ≥13 (revised per Amendment 02)
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary on the 7 most recent mornings (minimum 5 of 7 for eligibility) before the second screening visit, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that neither bedtime, (defined as the time the subject attempts to try to sleep), nor waketime (defined as the time the subject gets out of bed for the day) deviates more than 1 hour on more than 2 nights from the calculated MHB or median habitual waketime, respectively, from the Screening Sleep Diary entries
9. 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 second

screening visit, such that there is not more than 2 nights with time spent in bed duration < 7 hours or > 10 hours (revised per Amendment 02)

10. During the Run-in Period: Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary on the 7 most recent mornings before the first PSG during the Run-in Period, such that sWASO ≥ 60 minutes on at least 3 of the 7 nights
11. During the Run-in Period: Reconfirmation of regular bedtimes and waketimes as defined in Inclusion Criterion 8
12. During the Run-in Period: Reconfirmation of sufficient duration of time spent in bed as defined in Inclusion Criterion 9 (revised per Amendment 02)
13. During the Run-in Period: Objective (PSG) evidence of insomnia as follows: WASO average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes (revised per Amendment 02)
14. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
15. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

1. 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: (revised per Amendment 01)
   a. STOPBang score ≥5
   b. International Restless Legs Scale score ≥16
   c. Epworth Sleepiness Scale score >15 (Scores of 11-15 require excessive daytime sleepiness to be recorded in subject's Medical History) (revised per Amendments 01 and 02)
2. 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 (revised per Amendment 01)
3. On the MUPS, endorsed the item that corresponds to a history of sleep-eating or reports a history of sleep-related violent behavior, sleep-driving or symptoms of another parasomnia that in the investigator's opinion make the subject unsuitable for the study (revised per Amendment 02)
4. Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index > 15 as measured on the PSG at the second screening visit
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening

6. Beck Anxiety Inventory (BAI) score >15 at Screening
7. Habitually naps during the day more than 3 times per week
8. Is a female of childbearing potential

   Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, are in the appropriate age group, and are postmenopausal 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).
9. 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
10. History of drug or alcohol dependency or abuse within approximately the previous 2 years
11. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or habitually consumes alcohol within the 3 hours before bedtime and 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
12. Known to be positive for human immunodeficiency virus
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
14. A prolonged QT/QTcF interval (QTcF > 450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms)
15. Current evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal including severe hepatic impairment; renal including severe renal impairment; neurological including myasthenia gravis; psychiatric disease; 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, including the ability to perform tasks on the cognitive PAB. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. (revised per Amendment 01)
16. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
17. 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, including the ability to perform the PAB

18. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the eC-SSRS administration during the Prerandomization Phase (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)
19. Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS) (revised per Amendment 02)
20. Scheduled for surgery during the study
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period). (revised per Amendment 01) (A list of prohibited concomitant medications is presented in Appendix 3)
22. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period) (revised per Amendment 01)
23. Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study
25. A positive drug test at Screening, Run-In, or Baseline, or unwilling to refrain from use of recreational drugs during the study
26. Hypersensitivity to the study drugs (lemborexant or zolpidem) or to their excipients
27. 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
28. 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 ET Visit as soon as possible. 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 Treatment(s)

9.4.1 Treatment(s) Administered

Test drug

Lemborexant 5 mg, lemborexant 10 mg or lemborexant-matched placebo will be taken orally in tablet form at home each night for 30 consecutive nights, immediately before the time the subject intends to try to sleep.

Comparator drug

Zolpidem tartrate extended release 6.25 mg (Ambien CR®) or zolpidem-matched placebo will be taken orally in tablet form at home each night for 30 consecutive nights, immediately before the time the subject intends to try to sleep. The full Prescribing Information for Ambien CR will be provided to sites. (revised per Amendments 01 and 02)

Run-in Period

All subjects will receive 1 lemborexant-matched placebo tablet and 1 zolpidem-matched placebo tablet in a single-blind manner during the Run-in Period.

Treatment Period

During the Treatment Period, all subjects will receive 2 tablets as described below according to the treatment arm to which the subject has been randomized:

- LEM5: 1 zolpidem-matched placebo tablet and 1 lemborexant 5 mg tablet
- LEM10: 1 zolpidem-matched placebo tablet and 1 lemborexant 10 mg tablet
- ZOL: 1 zolpidem 6.25 mg tablet and 1 lemborexant-matched placebo tablet
- PBO: 1 zolpidem-matched placebo tablet and 1 lemborexant-matched placebo tablet

9.4.2 Identity of Investigational Product(s)

The sponsor will provide lemborexant tablets in strengths of 5 mg, 10 mg and lemborexant-matched placebo, identical in appearance. The comparator, zolpidem, will be obtained from commercial sources as zolpidem tartrate extended release 6.25 mg (Ambien CR 6.25) tablets, and the sponsor will provide placebo tablets identical in appearance to the zolpidem tablets. Tablets will be packaged in child-resistant 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 3. The subject will take 2 tablets a day; a single lemborexant or lemborexant-matched placebo tablet and a single zolpidem or zolpidem-matched placebo tablet. The placebo run-in card will contain a 17-day supply of lemborexant-matched placebo and zolpidem-matched placebo tablets per day. Each card for the Treatment Period will contain a 35-day supply of

tablets of either lemborexant or lemborexant-matched placebo and either zolpidem or zolpidem-matched placebo depending on the dose, in double-blind, double-dummy 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: C22H20F2N4O2
- Molecular weight: 410.42

9.4.2.2 Comparator Drug

Zolpidem tartrate extended release 6.25 mg (Ambien CR 6.25)

Placebos to match lemborexant or zolpidem tartrate extended release 6.25 mg

9.4.2.3 Labeling for Study Drug

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

The following information has to be provided:

- For clinical trial use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

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

9.4.3 Method of Assigning Subjects to Treatment Groups

At Baseline, subjects will be randomized, in a double-blind manner, to receive LEM5, LEM10, ZOL, or PBO in a 5:5:5:4 ratio. Randomization will be stratified by country and by age group (55 to 64 years; 65 years or older). Randomization to study treatments will be based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

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

9.4.4 Selection of Doses in the Study

In Study 201, all doses studied met the first primary objective of balancing significant efficacy as measured by change from baseline in SE with sufficient safety measured by subjective sleepiness reported on the KSS. The second primary objective was also achieved, as there were no significant increases in the KSS at 1 hour after waketime at the end of treatment. However, there were dose-related increases in the KSS at both the beginning and end of treatment, and the rate of AEs of somnolence also increased with increasing dose level.

In Study 201, lemborexant 5 mg and 10 mg showed significant efficacy measured by SE, as well as decreases in sleep onset latency. These effects were maintained across the 15-day Treatment Period. For sleep maintenance, lemborexant 10 mg showed significant decreases, and while the magnitude of decreases in WASO was less for 5 mg, there was a significant proportion of subjects whose WASO decreased substantially, providing evidence for clinical benefit of 5 mg on sleep maintenance as well.

Because of the observed dose-related increases in subjective sleepiness and AEs of somnolence in Study 201, Study 107 was conducted to obtain additional information about the risk of clinically meaningful morning residual sleepiness. The study assessed average sleep onset latency on the M-MSLT after a single dose of LEM5 or LEM10 versus PBO. The results indicated that the pre-specified threshold for a clinically meaningful decrease in average sleep onset latency was not met by either the 5 mg or 10 mg dose level of lemborexant, supporting their use in the Phase 3 clinical trials. Taken together with the efficacy and safety results for lemborexant 5 mg and 10 mg in the Phase 2 study, these dose levels were selected for the current study.

Regarding ZOL, the FDA-approved doses of Ambien CR are 6.25 mg (recommended dose for women and elderly patients) and 12.5 mg (highest recommended dose for non-elderly patients). In the present study, only the 6.25 mg dose of ZOL will be administered. Of note is that a maximum of 40% of the study sample will be in the age range of 55 to 64 years old, and stratification by age will be implemented to ensure that approximately 60% will be

65 years or older. All of the subjects in the 55 to 64 years age group will be females. (revised per Amendment 03)

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 immediately before the subject intends to sleep. When the subject is to sleep in the clinic for PSG, study personnel will administer study drug. On other nights, the subject will take study drug at home on as consistently a time schedule 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.

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

Disclosure of information from the interim analysis (Section 9.7.3) will be limited as detailed in the Interim Analysis charter. No individuals involved with the conduct of the study will have access to this information.

9.4.7 Prior and Concomitant Therapy

9.4.7.1 Drug-Drug Interactions

Not applicable

9.4.7.2 Prohibited Concomitant Therapies and Drugs

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 alcoholic drinks on any day during the study, and will be advised not to consume any alcohol within 3 hours before bedtime. They must not consume alcohol on any days when they are scheduled for a PSG recording. Compliance with these restrictions will be monitored via questions on the Sleep Diary. If subjects cannot comply after an infraction and counseling, they may be discharged from the study.

Prohibited medications include strong and moderate 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 above) 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).

A subject must discontinue any prohibited medication (Appendix 3) at least 1 week (or at least 5 half-lives, whichever is longer) before starting the Sleep Diary, ie, at least 2 weeks before the start of the Run-In Period.

Prohibited therapies include treatments for insomnia disorder (drugs or non-pharmacological treatment such as cognitive behavioral therapy) and any medication which, in the opinion of the investigator, causes or exacerbates the subject's insomnia. (revised per Amendment 01)

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 strong CYP3A inhibitors will not be permitted at any time for any duration of use during the study. (revised per Amendment 01)

Any medication (including over-the-counter medications) or therapy administered to the subject within the last 3 months before Screening (ie, Prior Medications) or during the study, starting on the date of informed consent, will be recorded on the Prior and Concomitant Medication 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.

9.4.8 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 within 5 minutes before bedtime, and they will be reminded that their bedtime should be the same throughout the study. Subjects will be told that following these instructions about taking study medication is important for the treatment to be effective. Compliance will be monitored closely and determined at specific visits by tablet count. Tablets will be counted separately for tablets that are matched to lemborexant and tablets that are matched to zolpidem.

When subjects arrive for the first screening/baseline PSG during the Run-in Period, and the treatment compliance check indicates that a subject has missed any doses, the subject will be counseled by site personnel. If the subject has missed more than 1 dose, and given that the subject continues to meet eligibility criteria, the investigator must consult with the sponsor prior to the subject being randomized and come to a collaborative decision on whether the subject should continue in the study. When subjects arrive for Baseline, and the treatment compliance check indicates that a subject has missed any doses, the investigator must use clinical judgment to decide if the subject should continue in the study.

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

9.4.9 Drug Supplies and Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572
- A signed and dated curriculum vita of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

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

The study drugs/ and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA; Medicine and Healthcare products Regulatory Agency. As applicable, all unused study drugs/ and empty and partially empty containers from used study drugs/ are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) 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. In some regions, study drugs/ may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

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

Study sites are also responsible for tracking receipt, distribution, and return of all study equipment (eg, Sleep Diary devices) to the sponsor or designated entity.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include date of birth, sex, and race/ethnicity (where allowed). In applicable countries, to protect personal data, only the year of birth will be collected, and the month and

date of each subject's date of birth will be masked where necessary as January 1. (revised per Amendment 01)

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Sleep, medical, and psychiatric history and current medical conditions will be recorded at the Screening Visit. All sleep, medical, and psychiatric history within 5 years must be noted in the Medical History and Current Medical Conditions eCRF. If a subject has a score of 11-15 on the ESS at Screening, then the presence of excessive daytime sleepiness must be recorded in the subject's Medical History. Note that the presence of excessive daytime sleepiness in a subject's Medical History, combined with the definition of Adverse Event as specified in Section 9.5.1.5.3 means that only a worsening in daytime sleepiness during the study should be reported as an Adverse Event. (revised per Amendment 02)

Physical examinations (full or brief) will be performed as described in Section 9.5.1.5.7.

9.5.1.2.2 Sleep Disorders History and Screening Battery

The SDSB will be administered only at the Screening Visit, and will include the:

- StopBANG: a list of eight questions to be answered Yes or No, which screens potential subjects for obstructive sleep apnea (Chung et al., 2008)
- IRLS: a subjective scale comprising ten questions, which measures disease of symptoms of restless legs syndrome (Abetz et al., 2006)
- ESS: a questionnaire that asks subjects to rate their probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, which assesses the severity of daytime sleepiness (Johns, 1992)
- MUPS: a scale comprising 21 questions asking whether the subject has experienced phenomena related to International Classification of Sleep Disorders Version 2 classified parasomnias (eg, enuresis, sleepwalking, sleep paralysis) along with a time frame for occurrences of these experiences ranging from within past month to lifetime and frequency within the time frame ranging from occasionally to almost every night (Fulda et al., 2008). An adapted version will be used. (revised per Amendment 01)

9.5.1.2.3 Beck Depression Inventory - II

The BDI-II is a 21-question multiple-choice self-report questionnaire that subjects will use to rate the presence, frequency, and severity of symptoms of depression using a 4-point Likert scale (Beck, et al., 1961). Scores on the BDI-II may range from 0 to 63, with higher scores indicating higher levels of depressive symptoms. Subjects with BDI-II scores greater than 19 will be excluded from participation.

9.5.1.2.4 BECK ANXIETY INVENTORY

The BAI is a 21-question multiple-choice self-report inventory that subjects will use to rate the presence, frequency, and severity of symptoms of anxiety using a 4-point Likert scale (Beck, et al., 1988). Scores on the BAI may range from 0 to 63, with higher scores indicating higher levels of anxiety symptoms. Subjects with scores on the BAI greater than 15 will be excluded from participation.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 POLYSOMNOGRAPHY

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

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

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

The following parameters will be derived from all PSGs:

- LPS: minutes from lights off to the first epoch of 20 consecutive epochs of non-wakefulness
- SE: proportion of time spent asleep per TIB, calculated as TST/interval from "lights off" until "lights on"
- WASO: minutes of wake from the onset of persistent sleep until lights on
- WASO2H: minutes of wake during the interval from 240 minutes after lights off until lights on
- TST: minutes of sleep from sleep onset until terminal awakening
- Mean duration of long awakenings (DurLongAw): average duration of all long awakenings (with long awakening defined as 10 or more consecutive epochs [ie, 5 minutes or longer] scored as wake or N1, initiated with at least 1 epoch of wake, after onset of persistent sleep, and including any terminal awakening

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

- Sleep onset latency: minutes from lights off to the first epoch of any stage of sleep (N1, N2, N3, REM) (revised per Amendment 01)
- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening cannot be interrupted by stage N1, but must be interrupted by stage N2, N3, or REM
- Number of long awakenings
- WASO1H (wake after sleep onset in the first half of the night): minutes of wake during the interval from onset of persistent sleep until 240 minutes after lights off (revised per Amendment 03)
- Percentage of sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: wake, NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of sleep (N1, N2, or N3) to first epoch of REM (revised per Amendment 01)

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

9.5.1.3.2 ELECTRONIC SLEEP DIARY

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-Up Period. Sleep Diary entries may be maintained in paper format as a backup to the electronic Sleep Diary, if necessary. This diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy and safety. (revised per Amendment 02)

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

Sleep Parameters

- Subjective Sleep Onset Latency (sSOL): estimated minutes from the time that the subject attempts attempting to sleep until sleep onset
- Subjective Wake After Sleep Onset (sWASO): sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stops trying to sleep for the night

- Subjective Total Sleep Time (sTST): derived minutes of sleep from sleep onset until the time the subject stops trying to sleep for the night
- Subjective Sleep Efficiency (sSE): proportion of sTST per subjective time spent in bed, calculated as the interval from the time that subject reports attempting to sleep until the time the subject stops trying to sleep for the night, and time spent asleep derived from subjective time spent in bed minus sWASO

Quality of Sleep

The Sleep Diary will also include items assessing sleep quality and morning sleepiness/alertness.

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

Morning Sleepiness

The Sleep Diary will also be used to assess subjective ratings of morning sleepiness with the following question: "How alert/sleepy do you feel this morning?" Subjects will rate their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely sleepy and 9 being extremely alert. (revised per Amendment 03)

The morning sleepiness question that is part of the electronic Sleep Diary will also be asked verbatim, using a paper-and-pencil format, at 1.5 hours after waketime each morning the subjects is in the clinic following a PSG recording. The rating on this question will be taken into consideration by the investigator when making the determination about whether it is safe for the subject to be discharged from the clinic.

Alcohol Consumption

The Sleep Diary will include questions that ask whether or not the subject consumed alcohol the previous day within 3 hours before bedtime or exceeded the daily maximum of 2 alcoholic drinks. (revised per Amendment 01)

9.5.1.3.3 INSOMNIA SEVERITY INDEX

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

9.5.1.3.4 FATIGUE SEVERITY SCALE

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS score is the sum of all responses to the 9 questions (Schwartz et al., 1993). Higher scores indicate greater fatigue.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

At predefined visits, a single, 4-mL blood sample per timepoint to determine plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) or zolpidem will be taken and will be processed according to instructions in a laboratory manual to be provided to the study sites. Plasma concentrations will be using validated liquid chromatography-tandem mass spectrometry assay methods. Concentrations of zolpidem will be determined only on an as needed basis as determined by the Study Director or Medical Monitor. The time and date of the 2 most recent doses preceding the samples obtained on Day 2 and Day 30 will be documented. (revised per Amendment 01)

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

Postural Stability using the CDR Posture Assessment

Postural stability will be assessed using an apparatus similar to the Wright ataxiameter, and referred to as the CDR posture device. This device measures directional trunk movements (ie, body sway) through a cord placed around the subject's waist and connected to the ataxiameter. On the evening of the Screening PSG visit, subjects will be introduced to the CDR posture assessment. Subjects will stand on a firm surface with feet comfortably apart, either barefoot or wearing socks. The standing position (inside heel-to-inside heel distance) and barefoot/socks conditions will be documented to ensure they remain the same for a given subject at each postural stability assessment timepoint. They will be instructed to stand as still as possible with eyes closed for 1 minute. (revised per Amendment 01) On the morning after the Screening PSG, subjects will complete a CDR posture assessment session for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, starting within 5 minutes of morning waketime, at bedside) as during the testing sessions at subsequent visits.

Body sway is detected through the cable around the subject's waist by the ataxiameter and these data are transmitted to a laptop. Body sway is measured in units of 1/3° of the angle of arc. For ease in reporting these will be called arbitrary units, with a higher number indicating more body sway (less postural stability).

Cognitive Performance Assessment Battery

A computerized PAB will be administered on a laptop computer after the postural stability test. (revised per Amendment 01) While completing the PAB, subjects will be in bed and ambient lighting will be maintained at a level of 80 to 100 lux at the subject's eye level. On the evening of the Screening PSG visit, before bedtime, subjects will be introduced to the PAB tasks and will undergo a minimum of 2 training sessions. If subjects cannot adequately perform the tasks during the training sessions, they will be excluded from further participation. On the morning after the Screening PSG, subjects will complete a session of the cognitive PAB for familiarization purposes only; no data from this session will be used for analyses. This session must be conducted under the same conditions (eg, lighting, subject in bed) as during the testing sessions at subsequent visits.

The PAB comprises 9 tasks, including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Word Recognition, Picture Recognition, Numeric Working Memory, and Spatial Working Memory. The full PAB will take approximately 18 to 30 minutes to complete. Four composite domain factor scores are calculated by combining outcome variables from the various tests, as described below:

- Power of Attention
  - A composite score from the speed scores of 3 tests of attention
  - Reflects the ability to focus attention and process information
- Continuity of Attention
  - A composite score created by combining the accuracy scores from the tests of attention
  - Reflects the ability to sustain attention (vigilance)
- Quality of Memory
  - A composite score created by combining the accuracy measures from the two tests of working memory and the four tests of episodic memory
  - Reflects the ability to store information in memory and subsequently retrieve it
- Speed of Memory Retrieval
  - A composite score created by combining the reaction time scores from the two working memory tests and the two episodic recognition tests
  - Reflects time taken to retrieve information held in both working and episodic memory

9.5.1.4.3 PHARMACOGENOMIC ASSESSMENTS

Not applicable

9.5.1.4.4 OTHER BIOMARKER ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. Safety will be assessed at every clinic visit throughout the study, and at the EOS Visit.

9.5.1.5.1 Columbia-Suicide Severity Rating Scale

Suicidality will be assessed using a self-rated electronic version of the eC-SSRS (Posner et al., 2011). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Qualified personnel must evaluate positive responses on the eC-SSRS and take appropriate action as detailed in the training and certification process for administering the eC-SSRS.

9.5.1.5.2 Tyrer Benzodiazepine Withdrawal Symptom Questionnaire

An assessment of withdrawal symptoms will be made using the T-BWSQ (Tyrer et al., 1990) to be completed at the EOS Visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes – moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's score. (revised per Amendment 02)

9.5.1.5.3 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 observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Serious adverse events (SAEs) will be collected for 28 days after the last dose.

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

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

It is the responsibility of the investigator to review the results of the eC-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5 for a description of the eC-SSRS).

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

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first.

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

ASSESSING SEVERITY OF ADVERSE EVENTS

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

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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.4) for the definition of an SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

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

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

CLASSIFICATION OF CAUSALITY

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

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

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

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

9.5.1.5.4 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of

SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

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

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

The following hospitalizations are not considered to be SAEs because there is no "AE" (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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.5 LABORATORY MEASUREMENTS

Clinical laboratory tests are to be performed according to the schedule in Table 2. Blood and urine samples will be collected for the clinical laboratory tests as listed in Table 3. Subjects should be in a seated or supine position during blood collection.

Viral testing for hepatitis B and C will be conducted from a blood sample obtained at Screening. The specific test for hepatitis B is the surface antigen panel (HBsAg) with confirmation as needed. The specific tests for hepatitis C are the hepatitis C virus (HCV) antibody immunoglobulin G (IgG), with confirmation as needed using the HCV score. (revised per Amendment 01)

A 30-mL urine sample for assessment of drugs of abuse will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 4). These samples will be tested for common drugs of use/abuse: eg, cocaine, cannabinoids, phencyclidine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines. (revised per Amendment 01)

Table 2 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 parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, globulin, glucose, iron, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Table 3 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments

	Volume per Sample Collection (mL)	Collection Time Points	Window Around Time Point	Volume Collected (mL)
Clinical laboratory tests	12[a]	Screening Baseline Day 31 EOS/ET	n/a	48
Viral tests	6[a]	Screening	n/a	6
PK sampling	4	Day 2 pm Day 3 am Day 30 pm Day 31 am	pm: within 2 hours predose am: after PAB and within 1 hour after morning waketime	16
Total Volume Collected				**70**

EOS = end of study, ET = early termination, n/a = not applicable, PK = pharmacokinetic

a. Estimated volume.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or two 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 9.5.1.5.3) and the case report form (CRF) Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs, the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Reporting of Serious Adverse Events, Section 9.5.4.1).

9.5.1.5.6 VITAL SIGNS AND WEIGHT MEASUREMENTS

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

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

9.5.1.5.7 PHYSICAL EXAMINATIONS

Physical examinations (full or brief) will be performed as designated in the Schedule of Procedures/Assessments Table 4). At Screening and at the end-of-study visit, a full physical examination will be conducted, including evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin. The full physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). A urogenital examination will only be required in the presence of clinical symptoms related to this region and at the discretion of the investigator. At other study visits as designated in Table 4, a brief physical examination will be conducted to assess health status by brief evaluation of the head, eyes, ears, nose, throat, heart, lungs, abdomen, and extremities, and other physical conditions of note. Documentation of the physical examinations, including the brief neurological examinations, will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE eCRF.

9.5.1.5.8 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 4).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.3). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

For ECG abnormalities meeting criteria of an SAE (see Section 9.5.1.5.4), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

9.5.1.5.9 OTHER ASSESSMENTS

EQ-5D-3L

The EQ-5D-3L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility (Brooks et al., 1996). The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

PATIENT GLOBAL IMPRESSION – INSOMNIA

The PGI-Insomnia questionnaire is a self-report assessment asking about a subject's perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a: helped/worsened sleep, b: decreased/increased time to fall asleep, and c: increased/decreased TST) and 1 item related to perceived appropriateness of study medication strength. The first 3 items are answered on a 3-point scale (1=positive medication effect, 2=neutral medication effect, 3=negative medication effect) and the last item on a different 3-point scale (medication: 1=too strong, 2=just right, 3=too weak). Each item will be reported separately. This scale was used in studies of zolpidem (Roth et al., 2006; Walsh et al., 2008).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

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

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-14/+4	-3/+4		-3/+3		-3/+3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-35 to -17	-17 to -10	-16 to -9	-10 to -4	-9 am to -3 am	-9 pm to -3 pm	-8 to -2	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
Demographics	X																			
Informed consent	X																			
Inclusion/exclusion criteria[f]	---------->																			
Height	X																			
Weight	X							X								X		X	X	
Clinical laboratory tests	X							X								X		X	X	X
Viral screening[g]	X																			
Vital signs	X							X								X		X	X	X
12-lead ECG	X							X								X		X	X	X
Sleep, medical, and psychiatric history	X																			
ISI	X			X				X								X				
SDSB[h]	X																			
Physical exam[i]	X															X		X	X	X
Prior / concomitant	---------->																			

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-14/+4	-3/+4		-3/+3		-3/+3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-35 to -17	-17 to -10	-16 to -9	-10 to -4	-9 am to -3 am	-9 pm to -3 pm	-8 to -2	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
medications																				
Beck Depression Inventory II	X																			
Beck Anxiety Inventory	X																			
Urine drug test	X	X		X		X		X			X		X		X					X
Postural stability		X[j]	X[k]		X		X			X		X		X		X				
Cognitive PAB		X[j]	X[k]		X		X			X		X		X		X				
FSS	X			X				X								X				
Morning Sleepiness			X		X		X			X		X		X		X				
Sleep Diary[l]		----------															----------	>		
EQ-5D-3L	X			X				X								X				
PK blood sampling[m]											X	X			X	X				X
eC-SSRS	X							X				X				X		X	X	X
Polysomnography[n]			X		X		X			X		X		X		X				

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

Phase	Prerandomization								Randomization											
Period	Screening			Run-in				BL	Treatment								Follow-Up		ET[e]	UN
Visit	1	2a	2b	3a	3b	4a[a]	4b	5a	5b	5c	6a[b]	6b	7a	7b	8a[c]	8b		EOS[d]		
Target Study Day	-21	-14	-13	-7	-6	-6	-5	1	1	2	2	3	29	30	30	31		44		
Window	-14/+4	-3/+4		-3/+3		-3/+3		n/a			n/a		-2/+5		-2/+5					
Possible Study Day(s) Given Window	-35 to -17	-17 to -10	-16 to -9	-10 to -4	-9 am to -3 am	-9 pm to -3 pm	-8 to -2	1	1 pm	2 am	2 pm	3 am	29 pm	30 am	30 pm	31 am	31 to 44	44		
Procedures/ Assessments																				
Randomization									X											
PGI-Insomnia																X				
T-BWSQ																		X	X	
Dispense study drug			X									X								
Study drug at bedtime[o]		→																		
Retrieve unused study drug								X					X							
Check study drug compliance[p]				X				X					X							
Admission to clinic		X		X		X		X			X		X		X					
Discharge from clinic			X		X		X			X		X		X		X				
Discharge from study																		X	X	
Adverse events[q]	→																			

(revised per Amendment 01)

Table 4 Schedule of Procedures/Assessments in Study E2006-G000-304

BL = baseline, eC-SSRS = electronic Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EMG = electromyography, EOS = end of study; ET = early termination, FSS = Fatigue Severity Scale, ISI = Insomnia Severity Index, PAB = performance assessment battery, PGI = Patient Global Impression, PK = pharmacokinetic, PSG = polysomnography, SDSB = Sleep Disorders Screening Battery, T-BWSQ = Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; UN = unscheduled visit.

a: Must be consecutive with Visit 3a.
b: Must be consecutive with Visit 5b.
c: Must be consecutive with Visit 7a.
d: Must occur 14 – 18 days after Visit 8.
e: Subjects who discontinue the study early for any reason after Randomization at Visit 5 should complete this visit.
f: Inclusion and exclusion criteria to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2.
g: Viral screening for hepatitis B (HBsAg) and hepatitis C (HCV antibody IgG) will be conducted. (revised per Amendment 01)
h: The Sleep Disorders Screening Battery includes: STOPBang, International Restless Legs Scale, Epworth Sleepiness Scale, and Munich Parasomnia Scale.
i: Full physical examination (including a brief neurological exam) will be carried out at Screening and EOS and ET (if applicable). Brief physical examinations will be carried out at other visits.
j: For training purposes only. Introduction to the CDR posture assessment and at least 2 training sessions of cognitive PAB to be completed before the end of Visit 2a. (revised per Amendment 02)
k: For familiarization purposes only. The CDR posture and cognitive PAB assessments are to be completed at Visit 2b under the same conditions as for testing at subsequent visits.
l: Should be completed, within 1 hour of morning waketime, on every day of the study from Screening until the end of the study, and reviewed for eligibility before initiating any study assessments at Visit 2 and Visit 3.
m: One PK blood sample (approximately 4 mL) will be obtained at the following timepoints: within 2 hours predose Day 2 and Day 30; within 1 hour after morning waketime on Day 3 and Day 31.
n: PSG recordings will include a standard montage on all PSG nights. Diagnostic channels (respiratory effort, airflow, leg EMG) will be added to the standard montage on the PSG at Visit 2. All PSG visits will require an overnight stay in the clinic. At least 2 nights must intervene between the second BL PGG (Visit 4b) and BL (Visit 5a). (revised per Amendment 02)
o: First dose of study drug is taken by the subject on the first night at home after Visit 2b. On the days that subjects are admitted to the clinic, study drug will be administered to the subject by clinical staff. The first dose of active study drug will be administered at Visit 5. On days that the subjects are not admitted to the clinic subjects will self-administer study drug. All study drug administration must be within 5 minutes of bedtime (defined as the time the subject attempts to sleep). (revised per Amendment 02)
p: Subjects will be questioned about study drug compliance upon check-in at Visits 3a, 5a, and 7a. Tablet counts for study drug compliance will be done after end of Run-in Period and end of Treatment Period.
q: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per Section 9.2.5 Adjudication Committee.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

Most of the clinical assessments are standard measurements commonly used in studies of drugs for the treatment of subjects with insomnia disorder.

Completion of sleep diaries by subjects is considered to be an appropriate method to measure changes in subjective sleep parameters, thereby allowing assessments of secondary efficacy in this study. The advantages of the electronic Sleep Diary to be used in this study include that the questions and instructional text have been adapted from sleep diaries that have were developed by clinicians and researchers with expertise in insomnia disorder, and have undergone linguistic validation and cognitive debriefing to optimize their use in this study. The Sleep Diary will include questions to assess the subject's rating of sleep quality each night and sleepiness/alertness level in the morning. The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. The FSS measures fatigue, which is another type of daytime impairment that is often a consequence of insomnia. This scale has been employed primarily in clinical trials of cognitive and behavioral treatments for insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of both nighttime sleep and daytime impairment complaints, the ISI and the FSS will be evaluated for changes from baseline. The PGI-Insomnia and EuroQoL assessment (version EQ-5D-3L) will also be employed. Both measures have been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life. Together these measures will provide a broad evaluation of the effects of lemborexant on each patient's sleep, daytime functioning, and quality of life.

The CDR posture and cognitive PAB will assess whether there are residual effects of study drug on morning postural stability and cognition. There are documented effects of hypnotic drugs, including zolpidem, on postural stability and certain cognitive domains in the morning hours. These effects are associated with an increased risk of falling and other negative effects on functioning in the morning hours. The measures to be employed to evaluate the effects on postural stability and cognition have been widely used in clinical trials of drugs in older individuals, including clinical trials of treatments for insomnia disorder.

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

9.5.4.1 Reporting of Serious Adverse Events

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

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

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

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

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

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Although the female subject population will be postmenopausal, in the event that a pregnancy does occur, investigators will capture and report such events.

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

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

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

aware of the pregnancy. (revised per Amendment 01) 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 after the time the investigator becomes aware of the outcome. (revised per Amendment 01)

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

9.5.4.3 Reporting of Events Associated with Special Situations

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. Investigators should report whether one or both study drugs had been taken incorrectly. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) 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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

For purposes of entering subject disposition in the eCRF, a subject will be considered to have completed the study per protocol after the End of Study visit has been completed. (revised per Amendment 01) For analysis purposes, a subject will be considered to have completed the study once the assessments on the morning after the last dose of study drug have been completed. All subjects will be required to return to the clinic at least 14, but not more than 18 days later for an End of Study (EOS) visit.

The investigator or subject may elect to discontinue the subject's participation in the study at any time for any reason. Subjects who discontinue study drug prematurely at any time after randomization at Visit 5 (Baseline) will be encouraged to return to the site as soon as possible (preferably within 7 days) to undergo an early termination (ET) Visit, as described in the Schedule of Procedures/Assessments (Table 4).

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

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, lack of therapeutic effect, or administrative/other. Discontinuations due to non-compliance with study drug, time spent in

bed, or alcohol restrictions will be assigned to "administrative/other." In addition to the primary reason, the subject may indicate one or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason will not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of one or both study drugs.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.4. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 must sign the completed eCRF 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 eCRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required.

The statistical analyses are described in this section. Further details of the statistical analyses will be included in a separate SAP.

All statistical tests will be based on the 5% level of significance (2-sided). If statistical comparisons are not defined, all pairwise comparisons will be tested.

9.7.1.1 Study Endpoints

Unless otherwise stated, the time points for Sleep Diary endpoints refer to the mean of the final 7 nights before the visit.

9.7.1.1.1 PRIMARY ENDPOINT(S)

The primary endpoint is:

- Change from baseline of mean LPS on Days 29 and 30 of LEM10 and LEM5 compared to PBO (revised per Amendment 03)

9.7.1.1.2 SECONDARY ENDPOINT(S)

Key Secondary Endpoints – US ONLY (revised per Amendment 03)

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO (revised per Amendment 04)
- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 and LEM5 compared to ZOL

Key Secondary Endpoints – Non-US ONLY (revised per Amendment 03)

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO

- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO

Additional Secondary Endpoints – US and Non-US (revised per Amendment 03)

- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, WASO, and TST on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 of LEM5 and LEM10 compared to PBO
- Change from baseline of mean WASO2H and TST on Days 29 and 30 of LEM5 and LEM10 compared to PBO
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO
- Proportion of responders on Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that
    - Objective sleep onset response is defined as LPS ≤ 20 minutes (provided mean baseline LPS was > 30 minutes)
    - Subjective sleep onset response is defined as sSOL ≤ 20 minutes (provided mean baseline sSOL was > 30 minutes)
    - Objective sleep maintenance response is defined as WASO ≤ 60 minutes (provided mean baseline WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
    - Subjective sleep maintenance response is defined as sWASO ≤ 60 minutes (provided mean WASO was > 60 minutes and is reduced by > 10 minutes compared to baseline)
- Safety and tolerability of LEM
- Change from baseline of the score from items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

9.7.1.1.3 EXPLORATORY ENDPOINT(S) – US AND NON-US (REVISED PER AMENDMENT 03)

The change from baseline of WASO2H for LEM5 and LEM10 compared to ZOL will be considered as exploratory for non-US. The following endpoints will be also explored for LEM5 and LEM10. Except for PK endpoints, comparisons to ZOL and PBO will be made. (revised per Amendment 03)

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
    - Change from baseline of sSOL at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights,mean sSOL of the second 7 nights (revised per Amendment 03)
    - Change from baseline of sWASO at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7, mean of the second 7 nights (revised per Amendment 03)
    - Proportion of subjects whose sSOL at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean for first 7 nights, mean of the second 7 nights (revised per Amendments 02 and 03)
    - Proportion of subjects whose sWASO is higher at Screening at the following timepoints during the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean for the first 7 nights, for thesecond 7 nights(revised per Amendments 02 and 03)
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period
- Change from baseline of mean morning sleepiness ratings assessed at 1.5 hours after waketime when subjects are in clinic on Days 1 and 2, and Days 29 and 30 (revised per Amendment 01)
- Change from baseline of mean minutes and mean percentage (a) per TIB and (b) per TST of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline of mean REM latency, mean number of awakenings, and mean number of long awakenings at Days 1 and 2 and Days 29 and 30 (revised per Amendment 03)

- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- Proportion of subjects who score ≥ 3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- PK of lemborexant and its metabolites M4, M9, and M10
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

9.7.1.2 Definitions of Analysis Sets

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

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

The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the SAP.

The PK Analysis Set is the group of subjects who have at least one quantifiable plasma concentration of lemborexant or its metabolites, or zolpidem, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least one quantifiable lemborexant concentration data point as per the PK Analysis Set.

9.7.1.3 Subject Disposition

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

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and BMI; categorical variables include sex, age group (55 – <65 years; 65 – <75 years; and 75 years or older), BMI group (less than 18.5, 18.5 to less than 25, 25 to 30, above 30), race and ethnicity. (revised per Amendments 03 and 04)

Characteristics of insomnia at Study Baseline will be summarized using Sleep Diary variables including sSOL, sWASO, sSE and sTST; PSG variables including LPS, WASO, SE, WASO2H and TST; ISI score and its individual question score, and FSS. The BDI-II and BAI scores will also be summarized at Study Baseline.

The above tables will be produced for the FAS if it differs from the Safety Analysis Set.

If sufficient numbers of subjects with a particular medical history (major depression, anxiety disorder, chronic pain, etc) are enrolled, demographic and other baseline characteristics will be summarized for each medical history group using descriptive statistics.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (Mar 2016 or latest version). The number (percentage) of subjects who take prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary-preferred term (PT). If the Safety Analysis Set and FAS differ substantially, then the prior and concomitant medication summaries will be repeated on the FAS.

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

Concomitant medications are defined as medications that (1) started before the first dose of randomized 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 randomized study drug to the last dose day plus 14 days. All medications will be presented in subject data listings. (revised per Amendment 02)

9.7.1.6 Efficacy Analyses

Where Sleep Diary endpoints are described, the first 7 nights of treatment refer to diary data entered on the first 7 mornings following the start of treatment; the last 7 nights of treatment refer to diary data entered on the last 7 mornings (up to and including the morning following the last PSG). Details of the handling of missing data for the various assessments will be addressed in the SAP.

Where PSG endpoints are described, Days 1 and 2 refer to the first two PSG recordings after start of treatment (scheduled on Visits 5 and 6), and Days 29 and 30 refer to the last two PSG recordings of the Treatment Period (scheduled on Visits 7 and 8).

Definition of Baseline

Baseline is defined as the means from the 2 PSGs during the Run-in period for PSG-derived variables; and the mean of the last 7 mornings before the first Baseline PSG during the Run-In Period for Sleep Diary variables. For other endpoints, baseline data are captured during the Run-in Period and Baseline Period. Details will be specified in the SAP.

Control of Type I Error (revised per Amendment 03)

A sequential gate-keeping procedure will be used for the primary and the key secondary endpoint comparisons to control for the overall type I error at the 0.05 significance level (Figure 2). The first endpoint comparison will be tested at the 0.05 significance level. If the testing is found to be statistically significant, then proceed to the next endpoint testing at significance level of 0.05, otherwise stop testing.

The primary endpoints will be tested in the following order:

- Change from baseline of the mean LPS of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean LPS of Days 29 and 30 of LEM5 compared to PBO

The key secondary endpoints will only be tested if both primary analyses are statistically significant at the 0.05 level. The key secondary endpoints will be tested in the following order:

US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO (revised per Amendment 04)
- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO (revised per Amendment 04)
- Change from baseline of the mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL

Non-US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO

- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO

No multiplicity adjustment will be done on other efficacy analyses.

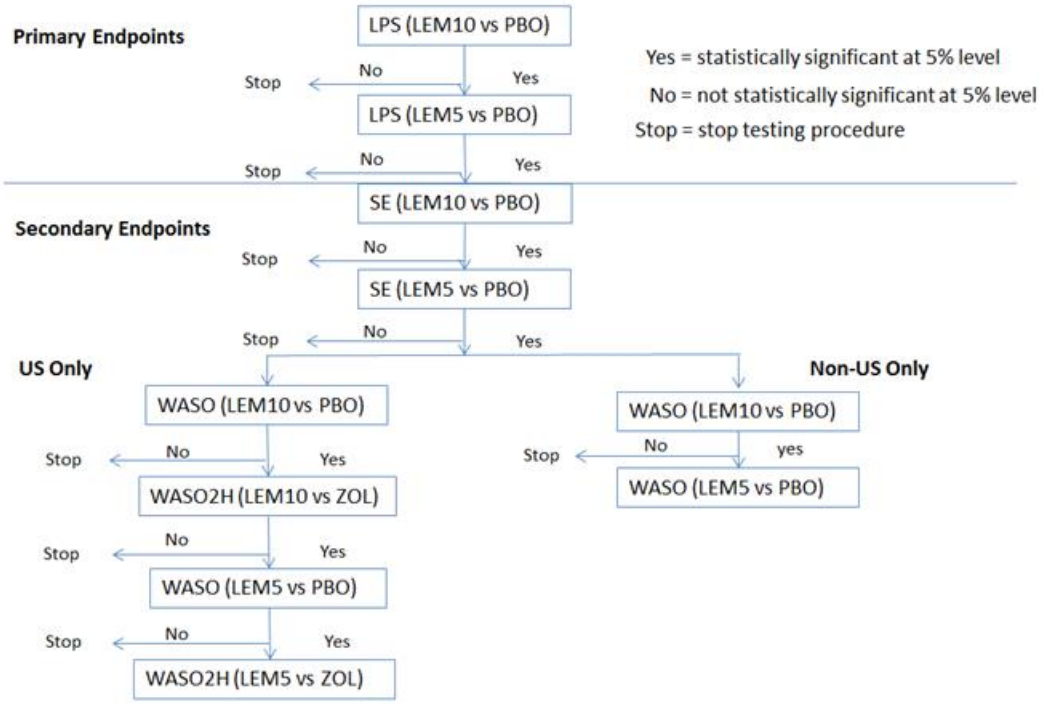


Figure 2 Flow Chart of Gate Keeping Testing Procedure – Study E2006-G000-304 (revised per Amendment 04)

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LPS = latency to persistent sleep, PBO = placebo, SE = sleep efficiency, US = Unites States, WASO = wake after sleep onset, WASO2H = wake after sleep onset in the second half of the night, ZOL = zolpidem tartrate extended release 6.25 mg.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Null Hypothesis: No difference exists in the mean change from baseline of the mean LPS of Days 29 and 30 for treatment with LEM10 (or LEM5) as compared with PBO. (revised per Amendment 03)

Alternative Hypothesis: A difference exists in the mean change from baseline of the mean LPS of Days 29 and 30 for LEM10 (or LEM5) compared to PBO. (revised per Amendment 03)

The LPS change from baseline (the mean of Days 1 and 2, and the mean of Days 29 and 30) will be analyzed using the mixed effect model repeated measurement analysis (MMRM) on the FAS. The model will include all data and will be adjusted for the corresponding baseline value (the means from the 2 PSG recordings during the Run-in Period), region, age group (55 – <65 years; 65 years or older), treatment, time (Days 1/2, and Days 29/30), and the interaction of treatment by time. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputations (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed primary efficacy assessments without missing values). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided. (revised per Amendments 03 and 04)

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

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described above will be repeated on subjects who completed all efficacy assessments and have no missing values.
- As-treated analysis: The same primary efficacy analyses described in Section 5.4.1 (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.
- MMRM analysis assuming missing at random (MAR): The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are MAR. (revised per Amendment 03)
- MI Imputation assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows): (revised per Amendment 04)

Study days where results are available	**1**	**2**	**29**	**30**
Pattern 1	x	x	x	x
Pattern 2	x	x	x	.
Pattern 3	x	x	.	.
Pattern 4	x	.	.	.
x = result present; . = result missing				

- Tipping point analysis: A range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant. (revised per Amendment 04)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Key Secondary Efficacy Analysis (revised per Amendments 03 and 04)

Changes from baseline of mean SE, WASO2H, and WASO of Days 1 and 2 and the mean of Days 29 and 30 will be analyzed using a pattern mixture model utilizing MI assuming MNAR. The treatment comparison will be performed using contrasts. The p-value, LS means and the 95% CI of the treatment differences will also be provided. The comparison of LEM10 and LEM5 to ZOL on WASO2H will be considered as exploratory for all non-US submissions. (revised per Amendment 03)

Other Secondary Efficacy Analysis (revised per Amendment 03)

The other secondary efficacy endpoints (change from baseline of the mean of the following endpoints: LPS, SE, WASO2H, and WASO of the mean of Days 1 and 2; TST of the mean of Days 1 and 2 and of the mean of Days 29 and 30; sSOL, sWASO, sSE, and sTST for the mean of the first 7 and last 7 days of the Treatment Period) will be analyzed using MMRM assuming MAR. (revised per Amendment 03)

The proportion of responders will be analyzed using the Cochran-Mantel-Haenszel test, controlled for region and age group, for each dose of lemborexant compared to PBO and ZOL. The analysis will be similarly repeated for responder analysis based on Sleep Diary variables (sSOL and sWASO) over the first 7 and last 7 nights of treatment. (revised per Amendment 03)

The change from baseline of the ISI total of four items on daytime functioning at Day 31 and the FSS score at Day 31 will be analyzed using analysis of covariance (ANCOVA), adjusted for the corresponding baseline value, age group, region, and treatment. (revised per Amendment 03)

Changes from baseline in mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval for the PAB tasks will be analyzed using MMRM assuming MAR. (revised per Amendments 01 and 03)

Secondary endpoints may also presented graphically or analyzed by modeling methods if warranted.

No multiplicity adjustment or missing value imputation is planned for other secondary analyses. (revised per Amendment 03)

9.7.1.6.3 EXPLORATORY EFFICACY AND PHARMACODYNAMIC ANALYSES

The change from baseline mean score of the quality of sleep item on the Sleep Diary for the means of the first 7 days and last 7 days of the Treatment Period will be analyzed using MMRM assuming MAR. (revised per Amendment 03)

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep Diary data from the Follow-up Period will be compared to Sleep Diary data from the Screening Period to assess whether subjects experience rebound insomnia. Specifically, a higher value for sSOL or sWASO during the Follow-up Period compared to the mean sSOL or sWASO value during the Screening Period will be considered worsened sleep. (revised per Amendments 01 and 02)

To assess rebound insomnia, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the first 3 nights, the mean of the first 3 nights, and the mean of each of the 2 weeks of the Follow-up Period the proportion of subjects whose corresponding value for sSOL or sWASO exceeds the corresponding Screening Period value by 5 minutes will be summarized by treatment group and compared to placebo. The percentage of 'rebounders' between each treatment and placebo group will be analyzed using a CMH test. (revised per Amendments 01, 02, and 03)

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for region, age group and treatment. The LS mean of each of the first 3 nights and each week of the Follow-up Period will be compared to the Screening Period between each treatment group and placebo. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. (revised per Amendments 01 and 03)

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning sleepiness item on the Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of the first 7 days and second 7 days of the Follow-up Period will be analyzed using MMRM assuming MAR. Change from baseline of the mean morning sleepiness ratings assessed at 1.5 hours after waketime when subjects are in clinic on days 1 and 2 and days 29 and 30 will be similarly analyzed using MMRM assuming MAR. (revised per Amendments 01 and 03)

The change from baseline of the mean of Days 1 and 2 and of the mean of Days 29 and 30 for the sleep architecture and other PSG endpoints (WASO1H, minutes and percentage [a] per TIB and [b] per TST of sleep stage N1, N2, N3, total NREM and REM; REM latency, DurLongAW, number of awakenings, number of long awakenings, REM episode frequency

and duration, and mean REM/NREM cycle duration) will be summarized. (revised per Amendment 03)

Each item on the PGI-Insomnia at Day 31 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

The change from baseline in the EQ-5D-3L score at Day 31 will be analyzed using ANCOVA, adjusted for region, age group and treatment. (revised per Amendment 03)

No multiplicity adjustment or missing value imputation is planned for exploratory and pharmocodynamic analyses. (revised per Amendment 03)

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, as well as zolpidem (where quantified) plasma concentration listings. The PK Analysis Set will be used for summaries of lemborexant and its metabolites M4, M9, and M10, as well as zolpidem (where quantified) plasma concentrations by dose, time and day.

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK analysis data from this study will be pooled with relevant data from Phase 1 and 2 studies, and other Phase 3 studies if available. To explore sources of variability in lemborexant PK, the effect of covariates (eg, demographics) on the PK of lemborexant will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC, $C_{max,}$ and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

<u>Pharmacodynamic Analyses</u>

These analyses are described in the Secondary Efficacy Analyses, and Exploratory and Pharmacodynamic Analyses sections (above).

<u>Pharmacokinetic/Pharmacodynamic Analyses</u>

The PK/PD relationship between exposure to lemborexant and efficacy variables including but not limited to LPS and WASO, and safety variables including but not limited to morning sleepiness and frequently occurring treatment-emergent adverse events (TEAEs), will be explored graphically. Any emergent PK/PD relationships will be evaluated by population PK/PD modeling. The population PK/PD analysis plan will be described and results will be reported in a separate document.

Population PK and PK/PD analyses will be performed using NONMEM version 7.2 or later.

Pharmacogenomic Analyses

Not applicable

Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

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, separately for each type of tablet. 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 eCRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings. AEs will be classified as TEAEs up to 14 days after the last study treatment.

Adverse events will be summarized by descriptive statistics, using the Safety Analysis Set. The TEAEs will be summarized by treatment group at the start of the TEAE. 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 during the Run-In Period will be summarized separately. The number (percentage) of subjects with TEAEs during the Treatment Period will be summarized separately. 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]). Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to the customized MedDRA query PT as potential cataplexy-related events, as well as somnolence and related events, and drug abuse liability will be summarized separately. (revised per Amendment 01)

9.7.1.8.3 CLINICAL LABORATORY VALUES

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

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

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

9.7.1.8.4 VITAL SIGNS, HEIGHT, AND WEIGHT

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from Study Baseline will be presented by visit and treatment group. Height will be measured once at Visit 1.

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range (Table 5). Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented for change from Study Baseline, by treatment group and by time point.

Table 5 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from Study Baseline will be presented by treatment group. Shift tables will present changes from Study Baseline in ECG interpretation (categorized as normal or abnormal) by time point. (revised per Amendment 02)

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

9.7.1.8.6 OTHER SAFETY ANALYSES

To evaluate morning residual sleepiness during study treatment and following completion of treatment, the change from baseline of the mean of morning residual sleepiness item on the Sleep Diary for the first 7 mornings of the Treatment Period, the last 7 mornings of the Treatment Period, as well as the means of each of the 2 weeks after treatment discontinuation will be analyzed using MMRM assuming MAR. (revised per Amendment 03)

The results of eC-SSRS assessments will be listed for each subject. The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group using descriptive statistics as appropriate.

Withdrawal symptoms will be assessed using the T-BWSQ. The mean score will be summarized by treatment group, and number (percentage) of subjects with a score ≥3 will be summarized.

Urine drug test results will also be listed.

9.7.1.9 Other Analyses

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

Although zolpidem is included in the study as an active comparator, comparison of ZOL to PBO, and comparison between LEM5 and LEM10 may be made to facilitate evaluation of study results.

9.7.2 Determination of Sample Size

The sample size was estimated for the each comparison of LEM10 vs. PBO, and LEM5 vs PBO with respect to the mean change from baseline of LPS at Month 1, on the basis of a 2-sided t-test at the 0.05 α-level for each treatment comparison. (revised per Amendment 03)

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the standard deviation (SD) of change from baseline for log-transformed LPS is assumed to be 0.9. The LS mean treatment difference at Days 14/15 from Study 201 for log-transformed LPS of LEM10 and LEM5 compared with PBO was 0.75 and -1.15, respectively. Therefore, a sample size of 250 subjects for LEM5, 250 subjects for LEM10, and 200 subjects for PBO has at least 95% power for each treatment comparison, LEM10 with PBO, and LEM5 with PBO, based on 2-sided, 2-sample t-test at 5% significance level. (revised per Amendment 03)

Power is also estimated for the key secondary objectives, the comparison of LEM10 and LEM5 to PBO on change from baseline of SE and WASO, and LEM10 and LEM5 to ZOL on WASO2H. A sample size of 250 subjects each for LEM5, LEM10, and ZOL, and 200 subjects for PBO has at least a 95% power for detecting a statistically significant difference between LEM and PBO for change from baseline in SE, at least 80% power for detecting a

statistically significant difference between LEM10 and ZOL/PBO for change from baseline in WASO/WASO2H based on 2-sided 2-sample t-test at 5% significance level. (revised per Amendments 03 and 04).

Table 6: Power and Sample Size Calculation for Change from Baseline of LPS, SE, WASO2H, and WASO

Endpoint (Test)	Estimated Treatment Difference	Estimated SD	Power
Log(LPS) (LEM5 vs PBO)	-0.75	0.9	>95%
Log(LPS) (LEM10 vs PBO)	-1.15	0.9	>95%
SE (LEM5 vs PBO)	5%	14%	>95%
SE (LEM10 vs PBO)	7%	14%	>95%
WASO (LEM5 vs PBO)	-10 min	55 min	48%
WASO (LEM10 vs PBO)	-15 min	55 min	81%
WASO2H (LEM5 vs ZOL)	-8 min	38 min	65%
WASO2H (LEM10 vs ZOL)	-11 min	38 min	89%

NOTE: Estimated treatment difference and SD are based on Study 201.

9.7.3 Interim Analysis

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the conditional power will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved with the conduct of the study will have access to the interim data or the results of the interim

analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis is concluded.

9.7.4 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

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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 (or if regionally required, the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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 and remote monitoring will be conducted between onsite monitoring visits by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, 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 eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

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, rhythm strips, EEGs, polysomnographs) regardless of how these images are stored, including microfiche and photographic negatives (revised per Amendment 01)
- Quality of life or medical history questionnaires completed by subjects (revised per Amendment 01)
- 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 dipsticks) (revised per Amendment 01)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

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

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

11.5 Identification of Source Data

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the

sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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

11.7 Auditing Procedures and Inspection

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

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, 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; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 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.

Schedule of Inclusion/Exclusion Criteria Assessments (revised per Amendment 02)

Visit Name	V1	V2	V3	V4	V5
	Screening	Screening 2	During Run-In Period	During Run-In Period	Baseline Period (just prior to Randomization)
Inclusion Criterion Number	I1, I2, I3, I4, I5, I6, I14, I15	I7, I8, I9	I6, I10, I11, I12, I13	I13	N/A
Exclusion Criterion Number	E1, E2, E3, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E23, E24, E25, E26, E27, E28	E4, E21 ,E22, E24, E25	E24, E25	E25	E24, E25

N/A = not applicable, V = visit.

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	o Barbiturates o Benzodiazepines o GABA analogues o Hydantoins o Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter)	o Diphenhydramine HCl o Carbinoxamine o Doxylamine o Dimenhyrinate o Triprolidine o Bromopheniramine o Chlorphenamine o Hydroxazine (revised per Amendment 02)
Antihistamines with known sedating effects	o *Non-sedating, eg, Claritin™ is not prohibited*
Anxiolytics with known sedating effects	o Lorazepam o Alprazolam o Buspirone
Strong CYP3A inhibitors	o Amiodarone o Bocepravir o Clarithomycin o Cobicistat o Conivaptan o Diltiazem o Danoprevir o Eltegravir o Fluvoxamine o Grapefruit juice o Idelalisib o Indinavir o Itraconazole o Ketoconazole o Lopinavir o Mibefradil o Nefazodone o Nelfinavir o Posaconazole o Ritonavir o Saquinavir o Telapravir o Telethromycin o Tipranavi o Troleandomycin o Voriconazole (revised per Amendment 02)

Category	Medication
Moderate CYP3A inhibitors	o Amprenavir o Aprepitant o Atazanavir o Casopitant o Cimetidine o Ciprofloxacin o Clotrimazole o Crizotinib o Cyclosporin o Darunavir o Dronadarone o Erythromycin o Faldaprevir o Fluconazole o Fluvoxamine o Imatinib o Netupitant o Tofisopam o Verapamil (revised per Amendment 02)
CYP3A inducers	o Avasimibe o Bosentan o Carbamazepine o Efavirenz o Enzaluteamide o Etravirine o Lersivirine o Modafinil o Mitotane o Nafcillin o Phenobarbital o Phenytoin o Rifabutin o Rifampin o St. John's Wort o Troglitazone o Talviraline o Thiroiridazine (revised per Amendment 02)
Hypnotics	o Melatonin o Prescribed or OTC
Herbal preparations with sedating effects	-
MAOIs	-
Opioid Analgesics	-
Muscle relaxants (centrally-acting) with known sedating effects	o GABA analogues o Hydantoins o Phenyltriazines
Stimulants	o Amphetamines o Modafinil o Armodafinil o Methylfenidate

Category	Medication
Other	○ Warfarin, heparin, ticlopidine ○ Non-stimulant diet pills ○ Systemic isoretinoin ○ Systemic glucocorticoids ○ Tryptophan (revised per Amendment 01)

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant
IND Number:	111,871
EudraCT Number:	2015-004347-39

SIGNATURES

Authors: (revised per Amendments 01, 02, and 03)

Patricia Murphy, PhD Study Director Associate Director, Clinical Research Neuroscience Business Group Eisai Inc.	Date
Gleb Filippov, MD Medical Monitor Director Neuroscience Business Group Eisai Ltd.	Date
Ishani Savant Landry, PhD Clinical Pharmacologist Director, Clinical Pharmacology and Translational Medicine Neuroscience Business Group Eisai Inc.	Date
Connie Chou, PhD Biostatistician Director, Biostatistics Neuroscience Business Group Eisai Inc.	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Investigational Product Name:	E2006/lemborexant
IND Number:	111,871
EudraCT Number:	2015-004347-39

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

Medical Institution

Investigator	Signature	Date

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Date:	20 June 2017
Version:	Final Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
AR	autoregressive covariance matrix
ATC	anatomical therapeutic class
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory - II
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
eC-SSRS	electronic version of Columbia-Suicide Severity Rating Scale
EOS	end of study
EQ VAS	visual analogue score from EQ-5D-3L questionnaire
FAS	full analysis set
FSS	Fatigue Severity Scale
LEM5	lemborexant 5 mg
LEM10	lemborexant 10mg
ISI	Insomnia Severity Index
LPS	latency to persistent sleep
LS	least squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing not at random
PAB	Performance Assessment Battery
PBO	placebo
PD	pharmacodynamic

Abbreviation	Term
PGI-Insomnia	Patient Global Impression - Insomnia
PK	pharmacokinetic
PSG	polysomnography
QTcB	corrected QT interval by Bazett's formula
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SE	sleep efficiency
SI	Système International
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
T-BWSQ	Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TIB	time in bed
TOEP	toeplitz covariance matrix
TST	total sleep time
UN	unstructured covariance matrix
WASO	wake after sleep onset
WASO1H	wake after sleep onset in the first half of the night
WASO2H	wake after sleep onset in the second half of the night
WHO DD	World Health Organization Drug Dictionary
ZOL	zolpidem artrate extended release 6.25 mg (Ambien CR®)

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2006-G000-304.

This document is prepared based on the final study protocol amendment 3 (dated 16Jun2017). Reader is referred to the study protocol, the case report form (CRF), general CRF completion guidelines for details of study design, conduct and data collection.

3.1 Study Objectives

3.1.1 Primary Objective - US and Non-US

Demonstrate using polysomnography (PSG) that lemborexant (LEM10 and LEM5) is superior to placebo (PBO) on sleep onset as assessed by latency to persistent to sleep (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder

3.1.2 Secondary Objectives

Key Secondary Objectives - US Only

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by sleep efficiency (SE) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to zolpidem artrate extended release 6.25 mg (Ambien CR®; ZOL) on wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of treatment

Key Secondary Objectives - Non-US Only

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by SE after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on wake after sleep onset (WASO) after the first 2 nights of treatment

Additional Secondary Objectives - US Only

- Demonstrate that lemborexant (LEM5 and LEM10) is superior to PBO on sleep maintenance as assessed by WASO after the last 2 nights of treatment

Additional Secondary Objectives - US and Non-US

- Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL on selected PSG variables after the first 2 nights and the last

2 nights of treatment and on selected Sleep Diary variables over the first 7 nights and the last 7 nights of treatment.

- Confirm the efficacy of LEM5 and LEM10 compared to PBO on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 and determine whether they are superior to that of ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary subjective sleep onset latency (sSOL) and subjective wake after sleep onset (sWASO)
- Evaluate the safety and tolerability of lemborexant
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) at the end of treatment
- Determine whether the safety of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO as assessed by cognitive performance in the morning after the first 2 nights of treatment

3.1.3 Exploratory Objectives - US and Non-US

- Explore the effects of LEM5, LEM10, ZOL and PBO on:
  - Subjective quality of sleep
  - Postural stability in the morning after the last 2 nights of treatment
  - Cognitive performance after the last 2 nights of treatment
  - Rebound insomnia in the 2 weeks following 30 days of treatment
  - Subjective ratings of morning sleepiness during and following completion of treatment
  - Sleep architecture parameters and other PSG variables
  - Health outcomes on the Patient Global Impression - Insomnia (PGI-Insomnia) and EQ-5D-3L
  - Withdrawal symptoms after completion of treatment
- Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Conduct population pharmacokinetic (PK) modeling for lemborexant
- Explore PK/pharmacodynamic (PK/PD) relationships between lemborexant concentrations and efficacy and safety variables

3.2 Overall Study Design and Plan

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males

65 years or older or females 55 years or older. Approximately 60% of the subjects will be age 65 years or older.

The study will have 2 phases: The Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 28 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights, and a minimum 14-day Follow-up Period before an End of Study (EOS) Visit.

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately 475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis Charter.

The study design is illustrated in Figure 1 below:

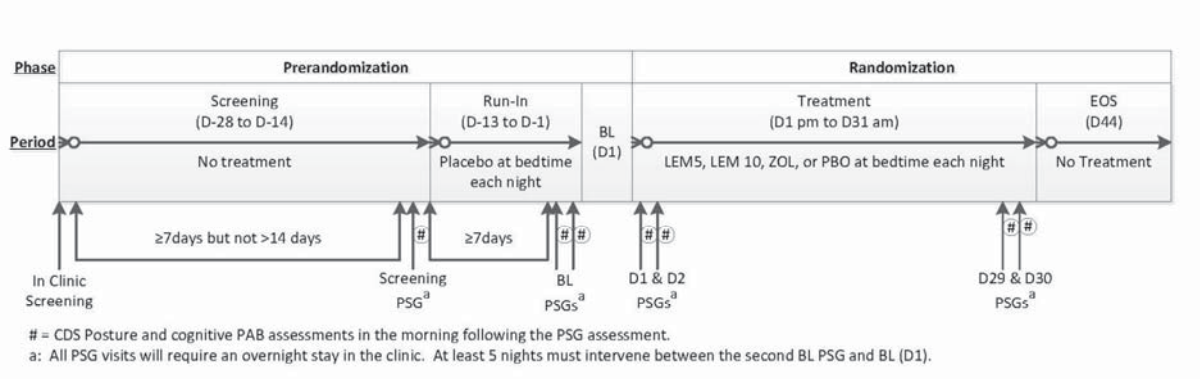

Figure 1 Study Design

"D" refers to the study day.
BL = baseline, EOS = End of Study, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PAB = performance assessment battery, PBO = placebo, PSG = polysomnography, ZOL = zolpidem tartrate extended release 6.25 mg.

4 DETERMINATION OF SAMPLE SIZE

The sample size was estimated for each comparison of LEM10 vs. PBO and LEM5 vs. PBO with respect to the mean change from baseline of LPS at Month 1, on the basis of a two-sided t-test at the 0.05 α-level for each treatment comparison.

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the standard deviation (SD) of change from baseline for log-tranformed LPS is assumed to be 0.9. The LS mean treatment difference at Days 14/15 from Study 201 for log-transformed LPS of LEM5 and LEM10 compared with PBO was -0.75 and -1.15, respectively. Therefore, a sample size of 250 subjects for LEM5, 250 subjects for LEM10, and 200 subjects for PBO has at least 95% power for each treatment comparison, LEM10 with PBO, and LEM5 with PBO, based on 2-sided 2-sample t-test at 5% significance level (Table 1).

Power is also estimated for the key secondary objectives, the comparison of LEM5 and LEM10 to PBO on change from baseline of SE and WASO, and LEM5 and LEM10 to ZOL on change from baseline of WASO2H (Table 1). A sample size of 250 subjects each for LEM5, LEM10, and ZOL, and 200 subjects for PBO has at least 95% power for detecting a statistically significant difference between LEM and PBO for change from baseline in SE, at least 80% power for detecting a statistically significant difference between LEM10 and ZOL/PBO for change from baseline in WASO2H/WASO based on 2-sided 2-sample t-test at 5% significance level.

Table 1: Power and Sample Size Calculation for Change from baseline of LPS, SE, WASO2H, and WASO

Endpoint (Test)	Estimated Treatment Difference	Estimated SD	Power
Log(LPS) (LEM5 vs PBO)	-0.75	0.9	>95%
Log(LPS) (LEM10 vs PBO)	-1.15	0.9	>95%
SE (LEM5 vs PBO)	5%	14%	>95%
SE (LEM10 vs PBO)	7%	14%	>95%
WASO2H (LEM5 vs ZOL)	-8 min	38 min	65%
WASO2H (LEM10 vs ZOL)	-11 min	38 min	89%
WASO (LEM5 vs PBO)	-10 min	55 min	48%
WASO (LEM10 vs PBO)	-15 min	55 min	81%

Estimated treatment difference and SD are based on Study 201.

5 STATISTICAL METHODS

All final statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

All descriptive statistics for continuous variables will be reported using number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number and percentage of subjects. In summaries for safety the denominator for all percentages will be the number of subjects in a given treatment.

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

5.1 Study Endpoints

5.1.1 Primary Endpoint(s)

The primary endpoint is:

- Change from baseline of mean LPS on Days 29 and 30 of LEM10 and LEM5 compared to PBO

5.1.2 Secondary Endpoint(s)

Key Secondary Endpoints - US Only

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 and LEM5 compared to ZOL

Key Secondary Endpoints - Non-US Only

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO

Additional Secondary Endpoints - US Only

- Change from baseline of mean WASO on Days 29 and 30 of LEM5 and LEM10 compared to PBO

Additional Secondary Endpoints - US and Non-US

- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, WASO, and total sleep time (TST) on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean subjective Sleep Diary variables including sSOL, sWASO, subject sleep efficiency (sSE) and subjective total sleep time (sTST) over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 of LEM5 and LEM10 compared to PBO
- Change from baseline of mean WASO2H and TST on Days 29 and 30 of LEM5 and LEM10 compared to PBO
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO
- Proportion of responders on Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that

  - Objective sleep onset response is defined as LPS ≤20 minutes (provided mean baseline LPS was >30 minutes)
  - Subjective sleep onset response is defined as sSOL ≤20 minutes (provided mean baseline sSOL was >30 minutes)
  - Objective sleep maintenance response is defined as WASO ≤60 minutes (provided mean baseline WASO was >60 minutes and is reduced by >10 minutes compared to baseline)
  - Subjective sleep maintenance response is defined as sWASO ≤60 minutes (provided mean WASO was >60 minutes and is reduced by >10 minutes compared to baseline)
- Change from baseline of the score from items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

5.1.3 Exploratory Endpoint(s) - US and Non-US

The change from baseline of WASO2H for LEM10 and LEM5 compared to ZOL is considered exploratory for non-US. The following endpoints will also be explored for LEM5 and LEM10. Except for PK endpoints, comparisons to both ZOL and PBO will be made.

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
  - Change from baseline of sSOL on each of the first 3 nights, mean sSOL of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
  - Change from baseline of sWASO on each of the first 3 nights, mean sWASO of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period

  - Proportion of subjects whose sSOL is longer than at Screening at the following time points during Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
  - Proportion of subjects whose sWASO is higher than at Screening at the following time points during Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period
- Change from baseline of mean morning sleepiness ratings assessed at 1.5 hours after wake time when subjects are in clinic on Days 1 and 2, and Days 29 and 30
- Change from baseline of mean minutes and mean percentage (a) per time in bed (TIB) and (b) per total sleep time (TST) of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline of mean REM latency, mean number of awakenings, and mean number of long awakenings at Days 1 and 2 and Days 29 and 30
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- Proportion of subjects who score ≥3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- PK of lemborexant and its metabolites M4, M9, and M10
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

5.1.4 Other Endpoints

The following PSG endpoints will be explored on an exploratory basis:

- Wake after sleep onset in the first half of the night (WASO1H)
- Duration of awakenings after persistent sleep
- Duration of long awakenings after persistent sleep
- Minutes and percentage of sleep stages per TIB: wake, non-REM (N1,N2, N3 separately and combined), REM

- Minutes and percentage of sleep stages per TST: wake, non-REM (N1,N2, N3 separately and combined), REM
- WASO by quarter of the night

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

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

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

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

Per Protocol Analysis Set (PP): The PP is the group of all randomized subjects who received protocol-assigned study drug and do not meet any of the following criteria:

- Subjects who have any major protocol violations (major inclusion/exclusion violations or other major protocol violations that impact the evaluation of efficacy)
- Subjects who use a prohibited concomitant medication (initial list of prohibited concomitant medication are described in the protocol) that affects the assessment of study endpoints
- Subjects who are non-compliant in terms of study medication

All potential major protocol deviations will be identified and reviewed in a blinded manner before database lock. A comprehensive list of subjects to be excluded from the PP will be agreed upon by the study team prior to database lock.

The number and percentage of subjects in each analysis set will be summarized by treatment groups using descriptive statistics. The summaries for FAS and PP will be based on subjects "as randomized". The summary for Safety Analysis Set will be based on subjects "as treated".

5.2.2 Subject Disposition

Subject disposition will be summarized by treatment group for all randomized subjects. The number and percentage of subjects who completed or discontinued prematurely from the study and their reason for discontinuation will be summarized by treatment group.

In addition, the number of subjects screened, the number and percentage of screen failures and their primary reason for screen failures will be summarized. The number and percentage

of randomized subjects will be summarized by geographic region, country and sites by treatment group for all randomized subjects. The number and percentage of subjects in each of the analysis sets will also be summarized.

5.2.3 Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to major/minor and standard classifications including but not limited to the following:

- Violations of inclusion/exclusion criteria
- Noncompliance with or incorrect implementation of protocol procedures
- Noncompliance of study drug/dosage intervention
- Use of prohibited concomitant medication

Major protocol deviations will be summarized by category and treatment group.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for FAS and Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and BMI; categorical variables include sex, age group (55 to 64, 65 to 74, ≥75 years), BMI group (<18.5, 18.5 to <25, 25 to 30, >30), race and ethnicity.

The selected baseline assessments of Sleep Diary variables including sSOL, sWASO, sSE and sTST; PSG variables including LPS, WASO, SE, WASO2H and TST; ISI score and its individual question score, and FSS will be summarized by treatment group. The BDI-II and BAI scores will also be summarized at study baseline.

MEDICAL HISTORY

All medical histories as documented by the Medical History and Current Medical Conditions CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percent of subjects with medical history will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD; Mar 2017 or latest version).

Prior medications are defined as medications that stopped before the first dose of study drug, including placebo during the Run-In Period. Concomitant medications are defined as medications that (1) started before the first dose of study drug (including the Run-In Period) 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 (including the Run-In Period) to the last dose day plus 14 days.

The number and percentage of subjects who take prior and concomitant medications will be summarized using the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class (ATC), and WHO DD preferred term (PT). If a subject takes the same medications for the same class level or drug name, the subject will be counted only once for that class level or drug name. Separate summary will be provided for subjects who take concomitant medication during Run-in Period and Treatment Period.

5.2.6 Treatment Compliance

Treatment compliance (in %) is defined as follows:

$$\frac{100 \times (\text{total number of tablets dispensed - total number of tablets returned or lost})}{\text{number of tablets expected to be taken}}$$

Treatment compliance during the Run-in and Treatment Period will be summarized separately using descriptive statistics based on Safety analysis set. Treatment compliance will also be summarized by treatment group using the categories <80%, >=80% to <=100%, >100% to <=120%, and >120%. In addition to overall treatment compliance, separate summaries will also be provided for tablets that are matched to LEM and tablets that are matched to ZOL.

5.3 Data Analysis General Considerations

The FAS will be used as the primary population for all efficacy analyses. The Per Protocol analysis set will be used for sensitivity analyses to corroborate the primary efficacy endpoints.

5.3.1 Pooling of Centers

This study was a multicenter, international study with an estimated 105 centers participated in the study. Due to small expected number of subjects in each center, sites will be pooled within specific geographic regions for primary and secondary efficacy analyses. Other analyses will be performed with all centers pooled across the study unless stated otherwise. Consistency of results across geographic regions will be examined as specified in the respective sections in this document.

5.3.2 Adjustments for Covariates

Baseline assessment and age groups (55 to 64, and ≥ 65 years old) are used as covariates in the primary and secondary analyses.

5.3.3 Multiple Comparisons/Multiplicity

A sequential gate-keeping procedure will be used for the primary and the key secondary endpoint comparisons to control for the overall type I error at the 0.05 significance level (Figure 2). The first endpoint comparison will be tested at the 0.05 significance level. If the testing is found to be statistical significant, then proceed to the next endpoint testing at significance level of 0.05, otherwise stop testing.

The primary endpoints will be tested in the following order:

- Change from baseline of the mean LPS of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean LPS of Days 29 and 30 of LEM5 compared to PBO

The key secondary endpoints will only be tested if both primary analyses are statistically significant at the 0.05 level. The key secondary endpoints will be tested in the following order:

US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL

Non-US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO

No multiplicity adjustment will be done on other efficacy analyses.

The gate-keeping testing procedure of the primary and secondary endpoints is illustrated in Figure 2 below:

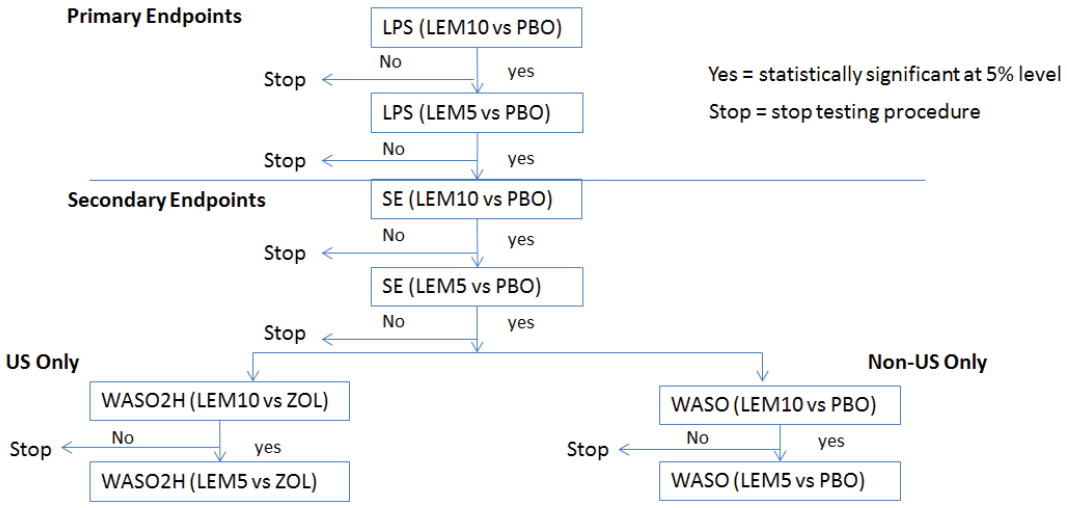

Figure 2 Flow Chart of Gate-Keeping Testing Procedure

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LPS = latency to persistent sleep, PBO = placebo, SE = sleep efficiency, WASO = wake after sleep onset, WASO2H = wake after sleep onset in the second half of the night, ZOL = zolpidem tartrate extended release 6.25 mg.

5.3.4 Examination of Subgroups

Subgroup analysis of primary and key-secondary efficacy endpoints will be performed using age group (55 to 64, 65 to 74, ≥75 years old), sex (male and female), race (white, black, Asian, and other), geographic region/country, and BMI group (<18.5, 18.5 to <25, 25 to 30, >30) as detailed in the respective sections in Sections 5.4, Efficacy/Pharmacodynamic Analyses.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Based on data on file and published clinical trials of similar mechanism (suvorexant, orexin antagonist), the percentage of missing values related to efficacy is expected to be minimal and unlikely to affect the result of the primary and secondary efficacy analyses. In the 1-month Phase 2 study of lemborexant (Study 201), the percentage of discontinued subjects from the lemborexant treatment group is expected to be approximately 5%. In suvorexant's Phase 3 program, the reported discontinuation rate due to lack of efficacy after 3 months of treatment was less than 2%.

The primary and key secondary efficacy endpoints will be analyzed using mixed effect model repeated measurement analysis (MMRM), the missing values will be imputed using pattern-mixture multiple imputation (MI) assuming the missing data is missing not at random (MNAR). As a sensitivity analysis, the primary efficacy endpoint will also be analyzed using MMRM assuming the missing data is missing at random (MAR).

Unless stated otherwise, missing values will be considered as non-responders in responder analyses and the continuous variables will be analyzed using MMRM assuming MAR. Details can be found in Sections 5.4, Efficacy/Pharmacodynamic Analyses.

All safety analyses will be performed based on the observed data only.

5.3.6 Other Considerations

The following estimands are evaluated for the primary efficacy endpoint (change from baseline in mean LPS on Days 29 and 30) in this study (Mallinckrodt, et al., 2012, and ICH, E9(R1) Final Concept Paper, 2014). The details of the analysis method are discussed in Section 5.4, Efficacy/Pharmacodynamic Analyses.

Estimand	**Description**	**Population**	**Intervention Effect of Interest**	**Analysis Type**
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values imputed using MI assuming MNAR (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.)***	primary
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values will not be imputed; MMRM model is used on all available data assuming MAR (Assumes subjects with missing values behave the same as the observed data within that treatment group, i.e., the missingness is independent of unobserved data after accounting for the observed data in the model. ***Thus the dropouts or subjects with missing values may continue to benefit from the treatment as if they were still on treatment (just like completers.))***	Sensitivity (MMRM analysis assuming MAR)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - subjects who complete the study without missing efficacy assessments	FAS	subjects who completed all efficacy assessments without missing values	Sensitivity (completer analysis)
Difference in outcome improvement for those who adhere to treatment	- subjects without major protocol violations that would impact efficacy assessments - include data after dropout	PP	missing values imputed using MI assuming MNAR (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.)***	sensitivity (PP analysis)
Difference in outcome improvement for those who adhere to treatment	- all randomized subjects; subject will be analyzed based on the actual treatment received - include data after dropout	FAS	missing values imputed using MI assuming MNAR (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective***	sensitivity (as-treated analysis)

Estimand	Description	Population	Intervention Effect of Interest	Analysis Type
			treatment group.)	
FAS = full analysis set; MI = multiple imputation; MAR = missing at random; MMRM = mixed effect model with repeated measurement; MNAR = missing not at random; PP = per-protocol analysis set; WASO2H = wake after sleep onset in the second half of the night				

5.4 Efficacy/Pharmacodynamic Analyses

Unless specified otherwise, all efficacy endpoints will be summarized and analyzed using FAS. Baseline values for each efficacy parameter are defined in Section 8.2, Baseline Assessment.

Unless specified otherwise, all efficacy/pharmacodynamic endpoints will be derived by calculating the averages of pairs of values [eg, average of LPS on Day 1 and Day 2 (denoted as Days 1/2 hereafter), average of LPS on Day 29 and Day 30 (denoted as Days 29/30 hereafter), …, etc.]

The primary and key secondary endpoints comparisons are tested following the gate-keeping testing procedure described in Section 5.3.3, Multiple Comparison/Multiplicity, to control for the overall type I error at the 0.05 significance level. The first primary efficacy endpoint comparison will be performed at the 0.05 significance level. The subsequent testings will only proceed if the previous test is statistically significant at the 0.05 level.

5.4.1 Primary Analyses

The primary efficacy endpoint is the change from baseline of LPS on Days 29/30 of LEM10 and LEM5 compared to PBO.

The null hypothesis of primary objective is that no difference exists in the mean change from baseline of LPS of Days 29/30 for treatment with LEM10 (or LEM5) as compared with PBO, and the corresponding alternative hypothesis is that a difference exists in the mean change from baseline of LPS of Days 29/30 for LEM10 (or LEM5) compared to PBO. The change from baseline of LPS on Days 1/2 and Days 29/30, will be analyzed using the mixed effect model repeated measurement analysis (MMRM) with factors of age group (55 to 64, and ≥ 65 years old), region (North America and Europe), treatment, visit (Days 1/2 and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline LPS as a covariate based on FAS. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. The unstructured covariance matrix (UN) will be used in the analysis. In the case of non-convergence of UN, the autoregressive [AR(1)] covariance matrix will be used in the model. Before the implementation of the MMRM model, the missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided.

Multiple Imputation

Step 1 (imputing missing data): Thirty multiple imputed complete datasets were to be constructed using the imputation regression model of age, sex, race (white, black, and other), and region (North America, and Europe), baseline BMI, baseline log(LPS), baseline ISI, baseline sSOL, and individual log(LPS) assessments on Days 1, 2 , 29, and 30, with a predefined arbitrary seed number (seed=2359). SAS PROC MI will be used to implement the imputation procedure using all available values. The dataset will be converted into monotone missing pattern by imputing arbitrary missing data as the first step. The monotone data will then be imputed with monotone regression method and MNAR. The sample SAS statement can be found in Section 9, Programming Specifications.

Step 2 (performing MMRM using each imputed dataset): The MMRM model with factors of age group (55 to 64, and ≥ 65 years old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline log(LPS) as a covariate will be applied to each imputed dataset. SAS PROC MIXED will be used for the MMRM analysis. The sample SAS statement can be found in Section 9, Programming Specifications.

Step 3 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 30 multiple imputed datasets from Step 2 will be combined using SAS PROC MIANALYZE to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules (Rubin DB, 1987). The sample SAS statement can be found in Section 9, Programming Specifications.

5.4.1.2 Subgroup Analyses

The primary endpoints described in Section 5.4.1 will be summarized using descriptive statistics by each subgroup listed below. No hypothesis testing will be performed in the subgroup analyses.

- Age group (55 to 64, 65 to 74, ≥75 years old)
- Sex (male and female)
- Race (white, black, Asian and other)
- Geographic region (North America and Europe)
- BMI group (<18.5, 18.5 to <25, 25 to 30, >30)

5.4.1.3 Sensitivity Analyses

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described in Section 5.4.1 (MMRM analysis with MI for missing value imputation) will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described in Section 5.4.1 (MMRM analysis without missing value imputation) will be repeated on subjects who completed all efficacy assessments and have no missing values.
- As-treated analysis: The same primary efficacy analyses described in Section 5.4.1 (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.
- MMRM analysis assuming MAR: The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are missing at random (MAR; MMRM analysis without missing value imputation).

5.4.2 Secondary Analyses

5.4.2.1 Key Secondary Analyses

CHANGE FROM BASELINE OF SE ON DAYS 29/30

The change from baseline of SE on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64, and ≥65 year old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline SE as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 5.4.1, Primary Analyses. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline SE, baseline ISI, baseline sSE, and individual SE assessments on Days 1, 2 , 29, and 30.

CHANGE FROM BASELINE OF WASO2H ON DAYS 29/30

The change from baseline of WASO2H on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64 years, and ≥ 65 year old), region (North America, and Europe), treatment, visit (Days

1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) covariance matrix will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 5.4.1, Primary Analyses. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline WASO2H, baseline ISI, baseline sWASO, and individual WASO2H assessments on Days 1, 2 , 29, and 30.

CHANGE FROM BASELINE OF WASO ON DAYS 29/30

The change from baseline of WASO on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64, and ≥65 year old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) covariance matrix will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 5.4.1, Primary Analyses. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline WASO, baseline ISI, baseline WASO, and individual WASO assessments on Days 1, 2 , 29, and 30.

The subgroup analyses described in Section 5.4.1.2 will be repeated for all key secondary endpoints.

5.4.2.2 Other Secondary Analyses

For all other secondary endpoints, the change from baseline assessments will be analyzed using MMRM assuming MAR (no missing value imputation) and the portion of responders will be analyzed using the Cochran Mantel Haenszel (CMH) test adjusted for age group. Missing values will be considered as non-responders in all responder analyses. No multiplicity adjustment will be made for all analyses.

POLYSOMNOGRAPHY

The following endpoints will be analyzed from PSG:

- Change from baseline of LPS, SE, WASO on Days 1/2 of LEM5 and LEM10 compared to PBO
- Change from baseline of LPS, SE, WASO on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of WASO2H on Days 1/2 of LEM5 and LEM10 compared to ZOL
- Change from baseline of WASO2H on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to PBO
- Change from baseline of WASO on Days 1/2 of LEM5 and LEM10 compared to PBO
- Change from baseline of WASO on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of TST on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL and PBO
- Proportion of responders on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL and PBO in which the responder is defined as follows:
    - Objective sleep onset responder: defined as LPS ≤20 minutes provided baseline LPS >30 minutes
    - Objective sleep maintenance responder: defined as WASO ≤60 minutes, a reduction from baseline by >10 minutes provided baseline WASO >60 minutes

ELECTRONIC SLEEP DIARY

The following endpoints will be analyzed from the Sleep Diary:

- Change from baseline of mean sSOL, sWASO, sTST, and sSE over the first 7 and last 7 nights of the treatment period of LEM 5 and LEM 10 compared to ZOL and PBO. The derivation of sSOL, sWASO, sTST and sSE is detailed in Appendix 13.2.

- Proportion of responders over the first 7 and last 7 nights of the treatment period of LEM5 and LEM10 compared to ZOL and PBO in which the responder is defined as follows:
  - Subjective sleep onset responder: defined as sSOL ≤20 minutes and baseline sSOL >30 minutes
  - Subjective sleep maintenance responder: defined as sWASO ≤60 minutes, reduction from baseline by > 10 minutes, and baseline sWASO >60 minutes

POSTURAL STABILITY USING THE CDR POSTURE ASSESSMENT

- Change from baseline of units of body sway on Days 2/3 of the Treatment Period compared to ZOL

INSOMNIA SEVERITY INDEX AND FATIGUE SEVERITY SCALE

The following endpoints will be analyzed from the ISI and FSS:

- Change from baseline of the total score from items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO

COGNITIVE PERFORMANCE ASSESSMENT BATTERY

The following endpoints will be analyzed from computerized performance assessment battery (PAB)

- Change from baseline of the 4 composite domain factor scores of PAB (power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval) on Days 2/3

5.4.3 Other Efficacy/Pharmacodynamic Analyses

The following endpoints are considered exploratory. Comparison of LEM10 and LEM5 will be made with ZOL and PBO.

Unless specified otherwise, for all other efficacy analyses endpoints, the change from baseline assessment will be analyzed using MMRM assuming MAR and the portion of responders will be analyzed using the Cochran Mantel Haenszel test adjusted for age group. Missing values will be considered as non-responders in all responder analyses. No multiplicity adjustment will be made for all analyses.

POLYSOMNOGRAPHY

- Change from baseline of total duration (in minutes) of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM on Days 1/2 and Days 29/30

- Percentage of the change from baseline of total duration of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM
  - per time in bed (TIB) on Days 1/2 and Days 29/30
  - per TST on Days 1/2 and Days 29/30
- Change from baseline of REM latency (defined as the first sleep epoch to first REM sleep epoch) on Days 1/2 and Days 29/30

  The change from baseline of mean REM latency will be analyzed separately for Days 1/2 and for Days 29/30 using Wilcoxon rank sum test. The treatment difference will be estimated using Hodges-Lehmann estimation, and the asymptotic (Moses) 95% CI for the difference will be provided.
- Change from baseline in number of awakenings on Days 1/2 and Days 29/30
- Change from baseline in number of long awakenings (defined as awakenings of 5 minutes or longer) on Days 1/2 and Days 29/30

ELECTRONIC SLEEP DIARY

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period
- Rebound insomnia endpoints during the Follow-up Period. Rebound insomnia is defined as worsened sleep (ie, higher value of sSOL or sWASO) relative to Screening after study drug treatment is completed.
  - Change from baseline of sSOL on each of the first 3 nights, mean of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
  - Change from baseline of sWASO on each of the first 3 nights, mean of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period
  - Proportion of subjects whose sSOL is longer than at Screening at the following time points of the Follow-up Period: each of the first 3 nights, mean of the first 3 night, mean of the first 7 nights, and mean of the second 7 nights
  - Proportion of subjects whose sWASO is higher than at Screening at the following time points of the Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, and mean of the second 7

  The actual value of sSOL and sWASO will be analyzed separately using analysis of covariance model (ANCOVA) with factors of age group (55 to 64, and ≥65 years older), region (North America, and Europe), and treatment for each time point (baseline, each of the first 3 night, mean of the first 3 nights, mean of the first 7 days, and mean of the last 7 days). The 95% CI of the treatment difference will be constructed for each time point. It will be considered as having strong evidence of rebound insomnia if the lower bound of the 95% CI of sSOL or sWASO for each of

the 3 night, the mean of the first 3 nights, mean of the first 7 days, and mean of the second 7 nights of the Follow-up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested.

- Mean rating on morning sleepiness over the first 7 mornings and last 7 mornings of the Treatment Period and over the first 7 mornings and last 7 mornings of the Follow-up Period.

MORNING SLEEPINESS QUESTIONNAIRE

- Change from baseline of morning sleepiness ratings on Days 1/2, and Days 29/30

POSTURAL STABILITY USING THE CDR POSTURE ASSESSMENT

- Change from baseline of units of body sway on Days 2/3 of the Treatment Period compared to PBO and on Days 30/31 of the Treatment Period compared to ZOL and PBO

COGNITIVE PERFORMANCE ASSESSMENT BATTERY

- Change from baseline of power of attention, continuity of attention, quality of memory, and speed of memory retrieval on Days 30/31

OTHER POLYSOMNOGRAPHY ASSESSMENTS

The following endpoints from PSG will also be summarized using frequency count or descriptive statistics by treatment groups for exploratory purpose. No hypothesis testing will be performed on these endpoints.

Unless specified otherwise, the following endpoints will be summarized for Days 1/2 and Days 29/30:

- WASO1H
- Number of awakenings after persistent sleep
- Number and duration of long awakenings after persistent sleep
- Minutes of sleep stages: WASO, non-REM (N1,N2, N3 separately and combined), REM
- Percentage of minutes for each sleep stages per TIB: WASO, non-REM (N1, N2, N3 separately and combined), REM
- Percentage of minutes for each sleep stages per TST: WASO, non-REM (N1, N2, N3 separately and combined), REM

- REM Latency (defined as the first sleep epoch to first REM sleep epoch)
- WASO by quarter (every 2 hours) of the night

5.5 Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The plasma concentrations of lemborexant and its metabolites M4, M9, and M10, as well as zolpidem (where quantified) will be summarized using descriptive statistics by dose, time and day based on Safety Analysis Set.

A separate analysis plan for the population PK analyses will be developed and finalized before the database lock.

5.5.2 Pharmacokinetic/Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

A separate analysis plan for the PK/PD analyses will be developed and finalized before the database lock.

5.6 Safety Analyses

All safety analyses will be performed based on observed data using the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics or frequency count only. No hypothesis testing will be performed for safety analyses.

5.6.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized using descriptive statistics by treatment group. Duration of exposure of study drug will be defined as the number of days between the date the subject received the first dose of study drug during Treatment Period and the date the subject received the last dose of study drug during Treatment Period, inclusive.

5.6.2 Adverse Events

The adverse event (AE) verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 20.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period), having been absent at pretreatment (before the Run-In Period) or

- Reemerges during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period), having been present at pretreatment (before the Run-In Period) but stopped before the last dose of study drug plus 14 days, or
- Worsens in severity during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period) relative to the pretreatment state, when the AE is continuous.

For TEAEs occurred during the Run-in Period, the incidence of TEAEs will be summarized by SOC and PT.

An overview table of TEAE occurred during Treatment Period, including number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), deaths, severe TEAEs, study drug related TEAEs, TEAEs leading to study drug withdrawal during the Treatment Period will be provided. In addition, the following summaries will be produced for the TEAEs occurred during the Treatment Period:

- Incidence of TEAEs by PT in descending order
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and severity
- Incidence of treatment-related TEAEs by SOC, PT, and severity
- Incidence of TEAEs by SOC, PT, and relationship to treatment

If a subject experiences more than one TEAE within a preferred term, the subject will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a subject experiences more than one TEAE within a SOC, the subject will be counted only once in the calculation of incidence of TEAE within that SOC. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence with the highest severity will be used in the calculation of the incidence of TEAE within that preferred term (SOC) by severity. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence considered most closely related to study drug will be used in the calculation of the incidence of TEAE with that preferred term (SOC) by relationship (given by investigator).

The following summaries will also be presented for the treatment-emergent SAEs occurred during the Treatment Period:

- Incidence of treatment-emergent SAEs by SOC and PT
- Incidence of treatment-emergent SAEs by SOC, PT, and relationship to treatment.

In addition, number and percentage of subjects with TEAEs and treatment-related TEAEs leading to discontinuation from study treatment during the Treatment Period will also be summarized by MedDRA SOC, PT for each treatment group.

5.6.2.1 Selected Adverse Events

The following significant AEs will be summarized by SOC and PT:

- Cataplexy
- Falls
- Seizures
- Abuse liability events

Cataplexy includes the TEAEs with MedDRA PT of cataplexy, and drop attack.

Falls includes the TEAEs with MedDRA PT of falls only.

Seizure includes TEAEs with MedDRA PTs belong to MedDRA Standardized MedDRA Queries (SMQ) of convulsions (narrow terms).

Abuse liability events includes TEAEs with MedDRA PT listed in Appendix 13.3.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. With the exception of urinalysis, all quantitative parameters listed in protocol Section 9.5.1.5.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline will be summarized at each visit using descriptive statistics by treatment group. For urinalysis, the actual and the change from baseline of pH and specific gravity will be summarized at each visit by treatment group. Analysis of changes from baseline 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. Shifts from baseline (LNH) to the Day 31 and the EOS visit will be provided by treatment groups for each laboratory parameter.

The Sponsor's Grading for Laboratory Values (Appendix 13.1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

For each vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, the actual value and changes from Study Baseline will be summarized by treatment group at each visit using descriptive statistics. Analysis of changes

from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

In addition, clinically notable vital sign values will be identified using the criteria in Table 1. The clinically notable vital sign values will be summarized using frequency count at each visit by treatment group.

Table 1 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L
Weight	--	Increase of ≥7%	H
	--	Decrease of ≥7%	L
Respiratory Rate	>20 bpm	--	H
	< 10 bpm	--	L

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

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

5.6.5 Electrocardiograms

For each ECG parameters (including PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval and heart rate) and actual value and changes from baseline will be summarized by treatment group at each visit using descriptive statistics. Shift tables from baseline to the Day 31 and the EOS visits will be presented by treatment group for ECG interpretation (categorized as normal and abnormal).

In addition, maximum postbaseline measurement will also be tabulated by treatment group as follows:

- Number and percentage of subjects with QTcF of >450 msec, and >500 msec during the treatment
- Number and percentage of subjects with a QTcF increment of >30 msec, and >60 msec from the baseline visit.
- Number and percentage of subjects with PR of >220 msec

- Number and percentage of subjects with QRS of >120 msec

5.6.6 Other Safety Analyses

5.6.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed using a self-rated electronic version of the C-SSRS (eC-SSRS). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. The incidence of suicidal ideation or suicidal behavior at each visit will be summarized by treatment group using frequency count.

5.6.6.2 Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ)

Withdrawal symptoms will be assessed using the T-BWSQ at the EOS visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes – moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's total score. The total score will be summarized by treatment group using descriptive statistics. In addition, the number and percentage of subjects with a total score of ≥3 will be summarized using frequency count.

5.7 Other Analyses

5.7.1 Health Outcome Economics Analyses

5.7.1.1 EQ-5D-3L

The EQ-5D-3L instrument comprises questions on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue score (EQ VAS). Each dimension has 3 levels: no problem, some problems, extreme problems and the EQ VAS is ranged from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state"). Each dimension score will be summarized separately at Baseline and Day 31 using frequency count on observed data only with no imputation. The change from baseline of EQ VAS will be analyzed using ANCOVA with factors of age group (55 to 64, and ≥65 years old), region (North America, and Europe), and treatment based on FAS.

5.7.1.2 Patient Global Impression (PGI) - Insomnia

The PGI-Insomnia questionnaire captures the global impression of the study medication's effect at the end of treatment and is collected on Day 31 visit only. The PGI-Insomnia has 3 items related to study medication effect (helped/worsened sleep, decreased/increased time to fall asleep, and increased/decreased TST) on a 3-point scale (1=positive medication effect, 2=neutral medication effect, and 3=negative medication effect) and 1 item related to perceived appropriateness of study mediation strength also on a 3-point scale (medication: 1=too strong, 2=just right, and 3=too weak). Each item will be analyzed summarized separately ("positive medication effect" versus others for the first 3 item; "just right" versus

others for the last item) using chi-square test on observed data only based on FAS with no imputation for missing values, and repeated for age subgroups.

5.8 Exploratory Analyses

None

6 INTERIM ANALYSES

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis Charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis Charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the interim results will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved with the conduct of the study will have access to the interim data or the results of the interim analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis is concluded.

7 CHANGES IN THE PLANNED ANALYSES

There is no change in the conduct or planned analysis from the protocol.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Visit Window

Study Day 1 is defined as the date of the first dose of study drug during the Treatment Period. The nominal visit (ie, study visit captured on the CRF) will be used as the analysis visits in all by-visit summaries. The Early Term visit will be considered as unscheduled visit and will not be included in the by-visit summary. Where applicable, the Early Term visit will be used along with the Day 31 visit for completers as the End of Treatment visit for the safety analyses.

8.2 Baseline Assessment

Unless otherwise specified, baseline measurement is the last observed measurement, including unscheduled assessments, prior to the first dose of study medication of treatment period for a given assessment. For the following endpoints, baseline measurement is defined as follows:

- PSG parameters : average of the two PSG recordings during the Run-in Period
- Sleep diary parameters:
  - For rebound insomnia: the mean of diary data entered on the last 7 mornings before the Screening PSG during the Screening Period
  - Other Sleep Diary-derived endpoints: the mean of diary data entered on the last 7 mornings before the first Baseline PSG during the Run-In Period
- Morning sleepiness questionnaire at 1.5 hours after wake time on mornings after PSG recordings: Average of the 2 morning sleepiness ratings during the Run-in Period
- ISI: Last available ISI measurement on or prior to Visit 5
- Postural Stability parameters: Average of non-missing measurements from Visit 3 Visit 4
- Cognitive PAB parameters: Average of non-missing measurements from Visit 3 and Visit 4
- FSS: Last available FSS measurement on or prior to Visit 5
- EQ-5D-3L: Last available EQ-5D-3L measurement on or prior to Visit 5

8.3 Missing Data Handling

Unless stated otherwise, missing values will be considered as non-responders in responder analyses and the continuous variables will be analyzed using MMRM to handle the missing values assuming MAR in all other efficacy analyses. Details can be found in Sections 5.4, Efficacy/Pharmacodynamic Analyses.

All safety analyses will be performed based on the observed data only.

8.3.1 Polysomnography, Cognitive Performance Assessment, Posture Stability, and Morning Sleepiness Questionnaire

Each PSG, PAB, posture stability, and morning sleepiness questionnaire parameters will be derived by calculating the averages of pairs of values, i.e., the average of the two PSG recordings during the Run-in Period, Day 1 and Day 2, and Day 29 and Day 30. If one of each pair of values is missing, the other available value will be taken as the average of the pair; if both values are missing, then the parameter will be missing for the corresponding pair.

8.3.2 Sleep Diary

Each Sleep Diary parameter will be derived by calculating the average of weekly (7 days) diary parameter values. For the follow-up period, if the first 7 nights overlaps with the last 7 nights (eg, the follow-up period is less than 14 days in total), the last non-overlaps nights will be used in calculating the average value for the last 7 nights.

For each Sleep Diary parameter at baseline, if no more than 2 of the 7 nights' values are missing, the available values will be used to calculate the mean. If more than 2 values are missing, the parameter will be considered missing for baseline. For each Sleep Diary parameter during treatment period and follow-up period, if at least 3 of the 7 nights' values are available, the available values will be used to calculate the mean. If less than 3 values are available, the parameter will be considered missing for the corresponding time point.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

The following sample SAS statement provides the framework for the MI method:

CONVERT DATASET INTO MONOTONE MISSING DATA PATTERN (IMPUTING ARBITRARY MISSING DATA):

```
PROC MI data=<dataset> nimpute=30 seed=2359 out=<dataset1>;
  VAR age BMI baseline… visit1-visit4;
  MCMC chain=multiple nbiter=500 niter=300 impute=monotone;
  BY treatment;
RUN;
```

IMPUTE MISSING VALUES:

```
PROC MI data=<dataset1> nimpute=1 seed=2359 out=<dataset2>;
  CLASS treatment sex race region;
  MONOTONE regression ( /details);
  MNAR model (visit1-visit4/ modelobs=CCMV);
```

```
  VAR treatment age sex race region BMI baseline….;
  BY _imputation_;
RUN;
```

PERFORMING MMRM:

```
PROC MIXED data=<dataset2>;
  CLASS subject treatment agegrp visit;
  MODEL value=treatment agegrp region visit visit*treatment / ddfm=kr;
  REPEAT visit/sub=subject type=UN;
  LSMEANS visit*treatment;
  ESTIMATE '5mg  –  ZOL Days 1_2'     treatment 0 -1 1 0  visit*treatment   0 0 -1 0 1 0 0 0/CL;
  ESTIMATE '10mg – ZOL Days 1_2'      treatment 0 -1 0 1  visit*treatment   0 0 -1 0 0 0 1 0/CL;
  ESTIMATE '5mg  –  ZOL Days 29_30'   treatment 0 -1 1 0  visit*treatment   0 0 0 -1 0 1 0 0/CL;
  ESTIMATE '10mg – ZOL Days 29_30'    treatment 0 -1 0 1  visit*treatment   0 0 0 -1 0 0 0 1/CL;
  BY _imputation_;
  ODS output estimates=<dataset3>;
RUN;
```

COMBINE RESULTS:

```
PROC MIANALYZE data=<dataset3>;
  MODELEFFECTS estimate;
  STDERR stderr;
RUN;
```

VARIABLE ORDER TO BE USED IN THE PROC MI PROCEDURES:

To Create Monotone Missing Data Pattern

- LPS: age, baseline BMI, baseline ISI, baseline log(sSOL), baseline log(LPS), log(LPS) at Day1, log(LPS) at Day2, log(LPS) at Day29, log(LPS) at Day30
- SE: age, baseline BMI, baseline ISI, baseline sSE, baseline SE, SE at Day1, SE at Day2, SE at Day29, SE at Day30
- WASO2H: age, baseline BMI, baseline ISI, baseline sWASO, baseline WASO2H, WASO2H at Day1, WASO2H at Day2, WASO2H at Day29, WASO2H at Day30
- WASO: age, baseline BMI, baseline ISI, baseline sWASO, baseline WASO, WASO at Day1, WASO at Day2, WASO at Day29, WASO at Day30

To Impute Missing Values

- LPS: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline log(sSOL), baseline log(LPS), log(LPS) at Day1, log(LPS) at Day2, log(LPS) at Day29, log(LPS) at Day30
- SE: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sSE, baseline SE, SE at Day1, SE at Day2, SE at Day29, SE at Day30

- WASO2H: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sWASO, baseline WASO2H, WASO2H at Day1, WASO2H at Day2, WASO2H at Day29, WASO2H at Day30
- WASO: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sWASO, baseline WASO, WASO at Day1, WASO at Day2, WASO at Day29, WASO at Day30

10 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or later versions). In the event that certain features graphical analyses cannot be implemented by SAS, other statistical software such as Splus can be employed.

The conditional power calculated for the interim analysis will be performed using EAST® version 6 (or later versions).

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and graphs shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

ICH Final Concept Paper E9(R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials dated 22October 2014.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharmaceutical Statistics 2012,11:456-461, 10 September 2012.Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

Sponsor's Grading for Laboratory Values

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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
	<LLN – 3.0 mmol/L	<3.0 – 2.2 mmol/L	<2.2 – 1.7 mmol/L	<1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

13.2 Derivations of Efficacy Endpoints from Electronic Sleep Diary

The following 7 questions are captured in the electronic Sleep Diary:

Q1: What time did you try to go to sleep?

Q2: How long did it take you to fall asleep?

Q3: How many times did you wake up, not counting your final awakening?

Q4: In total, how long did these awakenings last?

Q5: What time was your final awakening?

Q6: After your last awakening, how much longer did you try to sleep?

Q7: What time did you get out of bed for the day?

The efficacy endpoints from electronic Sleep Diary are defined as follows:

- sSOL= Q2
- sWASO = Q4 + Q6
- sTST = TIB – time spent awake [where TIB = Q7 – Q1; and time spent awake = Q2 + Q4 + Q6]
- sSE = sTST/TIB (as defined above)

13.3 List of Abuse Liability Events

Code	PT
10061422	Abnormal behaviour
10000125	Abnormal dreams
10063746	Accidental death
10000381	Accidental overdose
10000383	Accidental poisoning
10001022	Acute psychosis
10054196	Affect lability
10001443	Affective disorder
10001488	Aggression
10001497	Agitation
10001666	Alice in wonderland syndrome
10001854	Altered state of consciousness
10053549	Altered visual depth perception
10001949	Amnesia
10061423	Amnestic disorder
10002368	Anger
10002511	Anhedonia
10002711	Anterograde amnesia
10002820	Antisocial behaviour
10002855	Anxiety
10002942	Apathy
10003472	Asocial behaviour
10003739	Attention-seeking behaviour
10049848	Balance disorder
10004224	Belligerence
10005885	Blunted affect
10050012	Bradyphrenia
10057668	Cognitive disorder
10061046	Communication disorder
10010219	Compulsions
10010297	Confabulation
10067494	Confusional arousal
10010305	Confusional state
10050093	Consciousness fluctuating
10010947	Coordination abnormal
10012177	Deja vu
10012218	Delirium

10012239	Delusion
10012335	Dependence
10077805	Depersonalisation/derealisation disorder
10012374	Depressed mood
10012378	Depression
10012411	Derailment
10012422	Derealisation
10013142	Disinhibition
10013395	Disorientation
10013457	Dissociation
10013462	Dissociative disorder
10013468	Dissociative identity disorder
10013496	Disturbance in attention
10061108	Disturbance in social behaviour
10013573	Dizziness
10061111	Drug abuser
10013659	Drug administered at inappropriate site
10052237	Drug detoxification
10066053	Drug diversion
10052804	Drug tolerance
10052806	Drug tolerance increased
10079381	Drug use disorder
10013752	Drug withdrawal convulsions
10013753	Drug withdrawal headache
10013754	Drug withdrawal syndrome
10013887	Dysarthria
10054940	Dyslogia
10014551	Emotional disorder
10049119	Emotional distress
10048779	Energy increased
10015535	Euphoric mood
10070246	Executive dysfunction
10016256	Fatigue
10016275	Fear
10016322	Feeling abnormal
10016330	Feeling drunk
10016338	Feeling jittery
10016344	Feeling of despair
10016352	Feeling of relaxation
10016754	Flashback
10016759	Flat affect

10016777	Flight of ideas
10017062	Formication
10019063	Hallucination
10019070	Hallucination, auditory
10019072	Hallucination, olfactory
10062824	Hallucination, synaesthetic
10019074	Hallucination, tactile
10019075	Hallucination, visual
10019079	Hallucinations, mixed
10019133	Hangover
10020400	Hostility
10048533	Hypervigilance
10020937	Hypoaesthesia
10021212	Ideas of reference
10021402	Illogical thinking
10021403	Illusion
10049564	Impaired driving ability
10071176	Impaired reasoning
10049976	Impatience
10021567	Impulsive behaviour
10021588	Inappropriate affect
10021630	Incoherent
10021703	Indifference
10022523	Intentional overdose
10074903	Intentional product misuse
10023118	Jamais vu
10023236	Judgement impaired
10024264	Lethargy
10024825	Loose associations
10025429	Magical thinking
10026749	Mania
10027175	Memory impairment
10061284	Mental disorder
10027374	Mental impairment
10048294	Mental status changes
10027940	Mood altered
10027951	Mood swings
10028330	Muscle rigidity
10028747	Nasal necrosis
10028765	Nasal septum perforation
10028766	Nasal septum ulceration

10028896	Needle track marks
10061862	Neonatal complications of substance abuse
10029216	Nervousness
10029412	Nightmare
10033295	Overdose
10033664	Panic attack
10033670	Panic reaction
10033775	Paraesthesia
10033848	Paramnesia
10033864	Paranoia
10061910	Parasomnia
10063117	Paroxysmal perceptual alteration
10034719	Personality change
10061355	Poisoning
10067669	Prescription form tampering
10069330	Product tampering
10070592	Product used for unknown indication
10037211	Psychomotor hyperactivity
10037213	Psychomotor retardation
10049215	Psychomotor skills impaired
10061920	Psychotic disorder
10053632	Reactive psychosis
10038001	Rebound effect
10038743	Restlessness
10038965	Retrograde amnesia
10039897	Sedation
10040026	Sensory disturbance
10061567	Sensory level abnormal
10041052	Sluggishness
10041317	Somatic delusion
10062684	Somatic hallucination
10041349	Somnolence
10041953	Staring
10042264	Stupor
10067688	Substance abuser
10070964	Substance use
10079384	Substance use disorder
10072387	Substance-induced mood disorder
10072388	Substance-induced psychotic disorder
10042635	Suspiciousness
10043114	Tangentiality

10043431	Thinking abnormal
10043495	Thought blocking
10052214	Thought broadcasting
10043496	Thought insertion
10043497	Thought withdrawal
10070863	Toxicity to various agents
10044380	Transient global amnesia
10056326	Transient psychosis
10049414	Treatment noncompliance
10048010	Withdrawal syndrome
MedDRA 20.0	

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-G000-304
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo Controlled, Active Comparator, Parallel-Group Study of the Efficacy and Safety of Lemborexant in Subjects 55 Years and Older with Insomnia Disorder
Date:	05Feb2018
Version:	Final Version 3.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
AR	autoregressive covariance matrix
ATC	anatomical therapeutic class
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory - II
BMI	body mass index
CCMV	complete case missing value
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
eC-SSRS	electronic version of Columbia-Suicide Severity Rating Scale
EOS	end of study
EQ VAS	visual analogue score from EQ-5D-3L questionnaire
FAS	full analysis set
FSS	Fatigue Severity Scale
LEM5	lemborexant 5 mg
LEM10	lemborexant 10mg
ISI	Insomnia Severity Index
LPS	latency to persistent sleep
LS	least squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing not at random
PAB	Performance Assessment Battery
PBO	placebo

Abbreviation	Term
PD	pharmacodynamic
PGI-Insomnia	Patient Global Impression - Insomnia
PK	pharmacokinetic
PSG	polysomnography
QTcB	corrected QT interval by Bazett's formula
QTcF	corrected QT interval by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SE	sleep efficiency
SI	Système International
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
sSE	subjective sleep efficiency
sSOL	subjective sleep onset latency
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
T-BWSQ	Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TIB	time in bed
TST	total sleep time
UN	unstructured covariance matrix
WASO	wake after sleep onset
WASO1H	wake after sleep onset in the first half of the night
WASO2H	wake after sleep onset in the second half of the night
WHO DD	World Health Organization Drug Dictionary
ZOL	zolpidem tartrate extended release 6.25 mg (Ambien CR®)

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2006-G000-304.

This document is prepared based on the final study protocol amendment 4 (dated 05Feb2018). Reader is referred to the study protocol, the case report form (CRF), general CRF completion guidelines for details of study design, conduct and data collection.

1.1 Study Objectives

1.1.1 Primary Objective - US and Non-US

Demonstrate using polysomnography (PSG) that lemborexant (LEM10 and LEM5) is superior to placebo (PBO) on sleep onset as assessed by latency to persistent to sleep (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

1.1.2 Secondary Objectives

Key Secondary Objectives - US Only

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by sleep efficiency (SE) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by WASO after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to zolpidem tartrate extended release 6.25 mg (Ambien CR®; ZOL) on wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of treatment

Key Secondary Objectives - Non-US Only

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by SE after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on wake after sleep onset (WASO) after the last 2 nights of treatment

Additional Secondary Objectives - US and Non-US

- Demonstrate that LEM5 or LEM10 or both LEM5 and LEM10 are superior to ZOL on postural stability in the morning after the first 2 nights of treatment
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL on selected PSG variables after the first 2 nights and the last

2 nights of treatment and on selected Sleep Diary variables over the first 7 nights and the last 7 nights of treatment.

- Confirm the efficacy of LEM5 and LEM10 compared to PBO on sleep as measured by PSG after the first 2 and last 2 nights of treatment and as measured by Sleep Diary over the first 7 and last 7 nights of treatment
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 and determine whether they are superior to that of ZOL and PBO as defined by response on PSG LPS and WASO and Sleep Diary subjective sleep onset latency (sSOL) and subjective wake after sleep onset (sWASO)
- Evaluate the safety and tolerability of lemborexant
- Determine whether the efficacy of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO on daytime functioning as assessed by the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) at the end of treatment
- Determine whether the safety of LEM5 or LEM10 or both LEM5 and LEM10 is superior to that of ZOL and PBO as assessed by cognitive performance in the morning after the first 2 nights of treatment

1.1.3 Exploratory Objectives - US and Non-US

- Explore the effects of LEM5, LEM10, ZOL and PBO on:
    - Subjective quality of sleep
    - Postural stability in the morning after the last 2 nights of treatment
    - Cognitive performance after the last 2 nights of treatment
    - Rebound insomnia in the 2 weeks following 30 days of treatment
    - Subjective ratings of morning sleepiness during and following completion of treatment
    - Sleep architecture parameters and other PSG variables
    - Health outcomes on the Patient Global Impression - Insomnia (PGI-Insomnia) and EQ-5D-3L
    - Withdrawal symptoms after completion of treatment
- Summarize plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Conduct population pharmacokinetic (PK) modeling for lemborexant
- Explore PK/pharmacodynamic (PK/PD) relationships between lemborexant concentrations and selected efficacy and safety variables

1.2 Overall Study Design and Plan

E2006-G000-304 is a multicenter, randomized, double-blind, placebo-controlled, active comparator (ZOL), parallel-group study of 2 dose levels of lemborexant for 30 nights in approximately 950 subjects 55 years or older with insomnia disorder. Subjects will be males 65 years or older or females 55 years or older. Approximately 60% of the subjects will be age 65 years or older.

The study will have 2 phases: The Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to a maximum of 28 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects are treated for 30 nights, and a minimum 14-day Follow-up Period before an End of Study (EOS) Visit.

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately 475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis Charter.

The study design is illustrated in Figure 1.

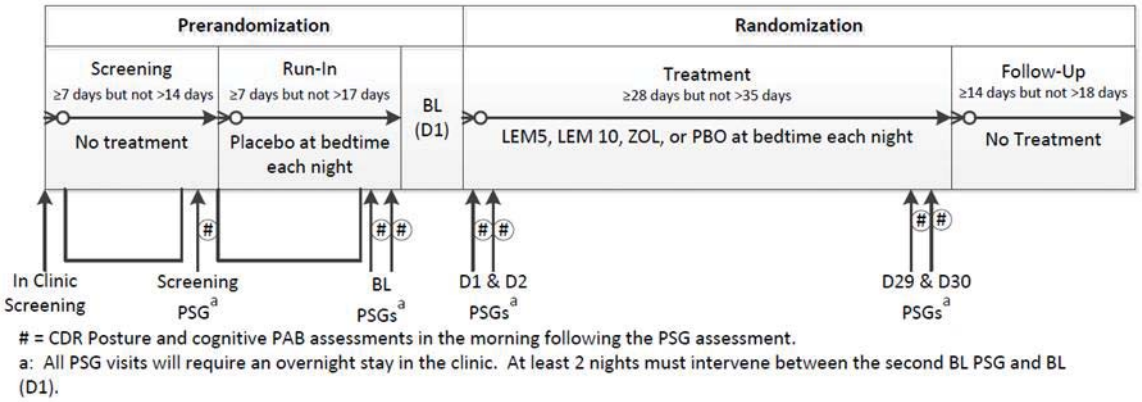

Figure 1 Study Design

"D" refers to the study day.
BL = baseline, EOS = End of Study, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PAB = performance assessment battery, PBO = placebo, PSG = polysomnography, ZOL = zolpidem tartrate extended release 6.25 mg.

2 DETERMINATION OF SAMPLE SIZE

The sample size was estimated for each comparison of LEM10 vs. PBO and LEM5 vs. PBO with respect to the mean change from baseline of LPS at Month 1, on the basis of a two-sided t-test at the 0.05 α-level for each treatment comparison.

On the basis of the dose finding study E2006-G000-201 (Study 201), across various lemborexant doses (1 to 25 mg) at Days 14 and 15, the standard deviation (SD) of change from baseline for log-transformed LPS is assumed to be 0.9. The LS mean treatment difference at Days 14/15 from Study 201 for log-transformed LPS of LEM5 and LEM10 compared with PBO was -0.75 and -1.15, respectively. Therefore, a sample size of 250 subjects for LEM5, 250 subjects for LEM10, and 200 subjects for PBO has at least 95% power for each treatment comparison, LEM10 with PBO, and LEM5 with PBO, based on 2-sided 2-sample t-test at 5% significance level (Table 1).

Power is also estimated for the key secondary objectives, the comparison of LEM5 and LEM10 to PBO on change from baseline of SE and WASO, and LEM5 and LEM10 to ZOL on change from baseline of WASO2H (Table 1). A sample size of 250 subjects each for LEM5, LEM10, and ZOL, and 200 subjects for PBO has at least 95% power for detecting a statistically significant difference between LEM and PBO for change from baseline in SE, at least 80% power for detecting a statistically significant difference between LEM10 and ZOL/PBO for change from baseline in WASO/WASO2H based on 2-sided 2-sample t-test at 5% significance level.

Table 1 Power and Sample Size Calculation for Change from Baseline of LPS, SE, WASO2H, and WASO

Endpoint (Test)	Estimated Treatment Difference	Estimated SD	Power
Log(LPS) (LEM5 vs PBO)	-0.75	0.9	>95%
Log(LPS) (LEM10 vs PBO)	-1.15	0.9	>95%
SE (LEM5 vs PBO)	5%	14%	>95%
SE (LEM10 vs PBO)	7%	14%	>95%
WASO (LEM5 vs PBO)	-10 min	55 min	48%
WASO (LEM10 vs PBO)	-15 min	55 min	81%
WASO2H (LEM5 vs ZOL)	-8 min	38 min	65%
WASO2H (LEM10 vs ZOL)	-11 min	38 min	89%

Estimated treatment difference and SD are based on Study 201.

3 STATISTICAL METHODS

All final statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

All descriptive statistics for continuous variables will be reported using number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number and percentage of subjects. In summaries for safety the denominator for all percentages will be the number of subjects in a given treatment.

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

3.1 Study Endpoints

3.1.1 Primary Endpoint(s)

The primary endpoint is:

- Change from baseline of mean LPS on Days 29 and 30 of LEM10 and LEM5 compared to PBO

3.1.2 Secondary Endpoint(s)

Key Secondary Endpoints - US Only

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO2H on Days 29 and 30 of LEM10 and LEM5 compared to ZOL

Key Secondary Endpoints - Non-US Only

- Change from baseline of mean SE on Days 29 and 30 of LEM10 and LEM5 compared to PBO
- Change from baseline of mean WASO on Days 29 and 30 of LEM10 and LEM5 compared to PBO

Additional Secondary Endpoints - US and Non-US

- Change from baseline on the postural stability test of mean units of body sway on Days 2 and 3 of LEM5 and LEM10 compared to ZOL

- Change from baseline of mean LPS, WASO, and total sleep time (TST) on Days 1 and 2 and Days 29 and 30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean subjective Sleep Diary variables including sSOL, sWASO, subject sleep efficiency (sSE) and subjective total sleep time (sTST) over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to ZOL
- Change from baseline of mean LPS, SE, WASO, WASO2H, and TST on Days 1 and 2 of LEM5 and LEM10 compared to PBO
- Change from baseline of mean WASO2H and TST on Days 29 and 30 of LEM5 and LEM10 compared to PBO
- Change from baseline mean of subjective Sleep Diary variables including sSOL, sWASO, sSE and sTST over the first 7 and last 7 nights of the Treatment Period of LEM5 and LEM10 compared to PBO
- Proportion of responders on Days 1 and 2 and Days 29 and 30 (PSG), and over the first 7 nights and last 7 nights of treatment (Sleep Diary), to LEM5 and LEM10 compared to ZOL and PBO, such that
    - Objective sleep onset response is defined as LPS ≤20 minutes (provided mean baseline LPS was >30 minutes)
    - Subjective sleep onset response is defined as sSOL ≤20 minutes (provided mean baseline sSOL was >30 minutes)
    - Objective sleep maintenance response is defined as WASO ≤60 minutes (provided mean baseline WASO was >60 minutes and is reduced by >10 minutes compared to baseline)
    - Subjective sleep maintenance response is defined as sWASO ≤60 minutes (provided mean WASO was >60 minutes and is reduced by >10 minutes compared to baseline)
- Change from baseline of the score from items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 2 and 3

3.1.3 Exploratory Endpoint(s) - US and Non-US

The change from baseline of WASO2H for LEM10 and LEM5 compared to ZOL is considered exploratory for non-US. The following endpoints will also be explored for LEM5 and LEM10. Except for PK endpoints, comparisons to both ZOL and PBO will be made.

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period

- Change from baseline of mean power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline of mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
    - Change from baseline of sSOL on each of the first 3 nights, mean sSOL of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
    - Change from baseline of sWASO on each of the first 3 nights, mean sWASO of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period
    - Proportion of subjects whose sSOL is longer than at Screening at the following time points during Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
    - Proportion of subjects whose sWASO is higher than at Screening at the following time points during Follow-up Period: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary on the first 7 mornings and second 7 mornings of the Follow-up Period
- Change from baseline of mean morning sleepiness ratings assessed at 1.5 hours after wake time when subjects are in clinic on Days 1 and 2, and Days 29 and 30
- Change from baseline of mean minutes and mean percentage (a) per time in bed (TIB) and (b) per total sleep time (TST) of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline of mean REM latency, mean number of awakenings, and mean number of long awakenings at Days 1 and 2 and Days 29 and 30
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- Proportion of subjects who score ≥3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at end of study
- PK of lemborexant and its metabolites M4, M9, and M10

- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

3.1.4 Other Endpoints

The following PSG endpoints will be explored on an exploratory basis:

- Wake after sleep onset in the first half of the night (WASO1H)
- Duration of awakenings after persistent sleep
- Duration of long awakenings after persistent sleep
- Minutes and percentage of sleep stages per TIB: wake, non-REM (N1, N2, N3 separately and combined), REM
- Minutes and percentage of sleep stages per TST: non-REM (N1, N2, N3 separately and combined), REM
- WASO by quarter of the night

3.2 Study Subjects

3.2.1 Definitions of Analysis Sets

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

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

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

Per Protocol Analysis Set (PP): The PP is the group of all randomized subjects who received protocol-assigned study drug and do not meet any of the following criteria:

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

- Incorrect study drug kit dispensed

Subjects who met any of the criteria listed above will be excluded from the PP due to possible introduction of bias.

The number and percentage of subjects in each analysis set will be summarized by treatment groups using descriptive statistics. The summaries for FAS and PP will be based on subjects "as randomized". The summary for Safety Analysis Set will be based on subjects "as treated".

3.2.2 Subject Disposition

Subject disposition will be summarized by treatment group for all randomized subjects. The number and percentage of subjects who completed or discontinued prematurely from the study and their reason for discontinuation will be summarized by treatment group.

In addition, the number of subjects screened the number and percentage of screen failures and their primary reason for screen failures will be summarized. The number and percentage of randomized subjects will be summarized by region, country and sites by treatment group for all randomized subjects. The number and percentage of subjects in each of the analysis sets will also be summarized.

3.2.3 Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock/treatment unblinding. All protocol deviations will be categorized according to major/minor and standard classifications including but not limited to the following:

- Violations of inclusion/exclusion criteria
- Noncompliance with or incorrect implementation of protocol procedures
- Noncompliance of study drug/dosage intervention
- Use of prohibited concomitant medication

Major protocol deviations will be summarized by category and treatment group.

3.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for FAS and Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and BMI; categorical variables include sex, age group (55 to <65, 65 to <75, ≥75 years), BMI group (<18.5, 18.5 to <25, 25 to 30, >30), race and ethnicity.

The selected baseline assessments of Sleep Diary variables including sSOL, sWASO, sSE and sTST; PSG variables including LPS, WASO, SE, WASO2H and TST; ISI score and its

individual question score, and FSS will be summarized by treatment group. The BDI-II and BAI scores will also be summarized at study baseline.

3.2.4.1 Medical History

All medical histories as documented by the Medical History and Current Medical Conditions CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percent of subjects with medical history will be summarized by System Organ Class (SOC), preferred term for each treatment group based on Safety Analysis Set.

3.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD; Mar 2017 or latest version).

Prior medications are defined as medications that stopped before the first dose of study drug, including placebo during the Run-In Period. Concomitant medications are defined as medications that (1) started before the first dose of study drug (including the Run-In Period) 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 (including the Run-In Period) to the last dose day plus 14 days.

The number and percentage of subjects who take prior and concomitant medications will be summarized using the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class (ATC), and WHO DD preferred term (PT). If a subject takes the same medications for the same class level or drug name, the subject will be counted only once for that class level or drug name. Separate summary will be provided for subjects who take concomitant medication during Run-in Period and Treatment Period.

3.2.6 Treatment Compliance

Treatment compliance (in %) is defined as follows:

$$\frac{100 \times (\text{total number of tablets dispensed} - \text{total number of tablets returned or lost})}{\text{number of tablets expected to be taken}}$$

Treatment compliance during the Run-in and Treatment Period will be summarized separately using descriptive statistics based on Safety analysis set. Treatment compliance will also be summarized by treatment group using the categories <80%, ≥80% to ≤100%, >100% to ≤120%, and >120%. In addition to overall treatment compliance, separate summaries will also be provided for tablets that are matched to LEM and tablets that are matched to ZOL.

3.3 Data Analysis General Considerations

The FAS will be used as the primary population for all efficacy analyses. The Per Protocol analysis set will be used for sensitivity analyses to corroborate the primary efficacy endpoints.

3.3.1 Pooling of Centers

This study was a multicenter, international study with an estimated 105 centers participating in the study. Due to small expected number of subjects in each center, sites will be pooled within specific regions for primary and secondary efficacy analyses. Other analyses will be performed with all centers pooled across the study unless stated otherwise. Consistency of results across regions (North America and Europe) will be examined as specified in the respective sections in this document.

3.3.2 Adjustments for Covariates

Baseline assessment and age groups (55 to 64, and ≥ 65 years old) are used as covariates in the primary and secondary analyses.

3.3.3 Multiple Comparisons/Multiplicity

A sequential gate-keeping procedure will be used for the primary and the key secondary endpoint comparisons to control for the overall type I error at the 0.05 significance level (Figure 2). The first endpoint comparison will be tested at the 0.05 significance level. If the testing is found to be statistical significant, then proceed to the next endpoint testing at significance level of 0.05, otherwise stop testing.

The primary endpoints will be tested in the following order:

- Change from baseline of the mean LPS of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean LPS of Days 29 and 30 of LEM5 compared to PBO

The key secondary endpoints will only be tested if both primary analyses are statistically significant at the 0.05 level. The key secondary endpoints will be tested in the following order:

US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO

- Change from baseline of the mean WASO2H of Days 29 and 30 of LEM10 compared to ZOL
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO2H on Days 29 and 30 of LEM5 compared to ZOL

Non-US Only

- Change from baseline of the mean SE of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean SE of Days 29 and 30 of LEM5 compared to PBO
- Change from baseline of the mean WASO of Days 29 and 30 of LEM10 compared to PBO
- Change from baseline of the mean WASO on Days 29 and 30 of LEM5 compared to PBO

No multiplicity adjustment will be done on other efficacy analyses.

The gate-keeping testing procedure of the primary and secondary endpoints is illustrated in Figure 2:

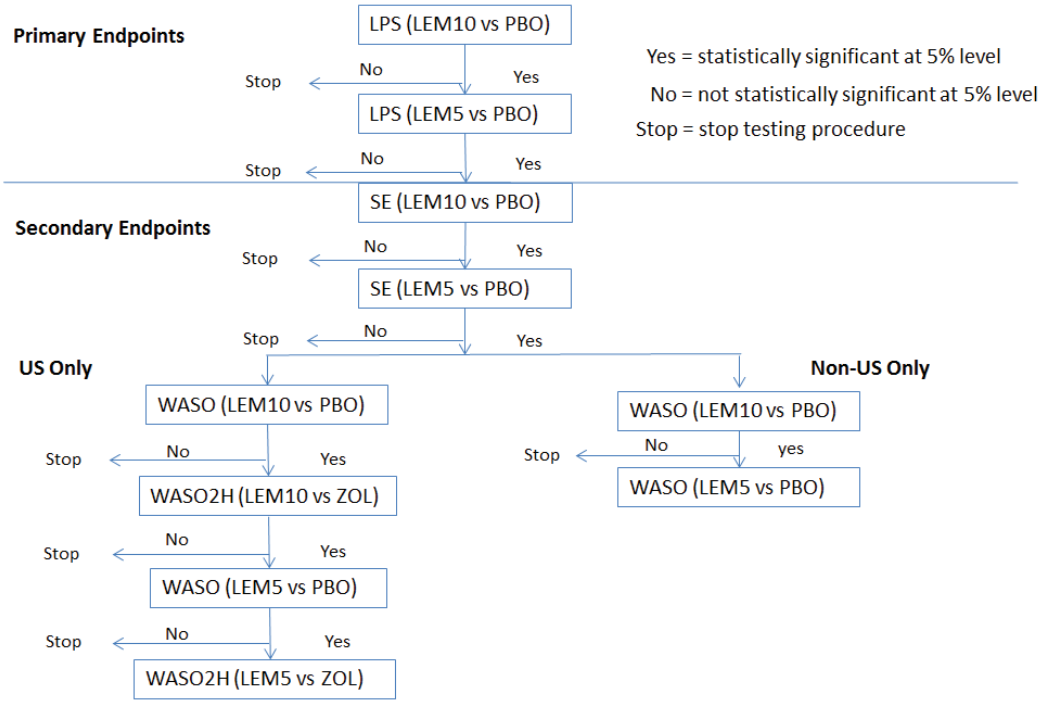

Figure 2 Flow Chart of Gate-Keeping Testing Procedure

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LPS = latency to persistent sleep, PBO = placebo, SE = sleep efficiency, WASO = wake after sleep onset, WASO2H = wake after sleep onset in the second half of the night, ZOL = zolpidem tartrate extended release 6.25 mg.

3.3.4 Examination of Subgroups

Subgroup analysis of primary and key-secondary efficacy endpoints will be performed using age group (55 to <65, 65 to <75, ≥75 years old), alternative age group (55 to <65, ≥65 years old), sex (male and female), race (white, black, Asian, and other), region (North America and Europe), and BMI group (<18.5, 18.5 to <25, 25 to 30, >30) as detailed in Section 3.4.

3.3.5 Handling of Missing Data, Dropouts, and Outliers

Based on data on file and published clinical trials of similar mechanism (suvorexant, orexin receptor antagonist), the percentage of missing values related to efficacy is expected to be minimal and unlikely to affect the result of the primary and secondary efficacy analyses. Based primarily on data from the 1-month Phase 2 study of lemborexant (Study 201), the percentage of discontinued subjects from the lemborexant treatment group is expected to be approximately 5%. In suvorexant's Phase 3 program, the reported discontinuation rate due to any reason within 3 month of treatment was 8%, including less than 2% who discontinued due to lack of efficacy

The primary and key secondary efficacy endpoints will be analyzed using mixed effect model repeated measurement analysis (MMRM), the missing values will be imputed using

pattern-mixture multiple imputation (MI) assuming the missing data is missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV). Additional sensitivity analyses will also be performed on primary and key secondary efficacy endpoints as follows:

MI Methods	Details	Analysis Type
Complete Case Missing Value (CCMV)	Subjects with missing data at any day are assumed to have a similar distribution as the ***completers within the respective treatment group*** (Pattern 1, below), where completers are defined as having no missing assessments for any post-baseline visits	Primary
Complete Case-4 CCMV(k=4)	This MI method will use all available monotone missing patterns to impute missing data assuming MNAR. This will relax the assumption of using only the complete cases as in the primary analysis. Study days where results are available: 1 2 29 30 Pattern 1: x x x x Pattern 2: x x x . Pattern 3: x x . . Pattern 4: x . . .	Sensitivity
Tipping Point	Imputation towards the null hypotheses: A range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant.	Sensitivity

Unless stated otherwise, missing values will be considered as non-responders in responder analyses and the continuous variables will be analyzed using MMRM assuming MAR. Details can be found in Section 3.4.

All safety analyses will be performed based on the observed data only.

3.3.6 Other Considerations

The following estimands are evaluated for the primary and key secondary efficacy endpoints in this study (Mallinckrodt, et al., 2012, and ICH E9(R1) Final Concept Paper, 2014). The details of the analysis method are discussed in Section 3.4.

Estimand	Description	Population	Intervention Effect of Interest	Analysis Type
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values imputed using MI assuming MNAR utilizing CCMV missing value pattern (complete cases) (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.***)	primary

Estimand	Description	Population	Intervention Effect of Interest	Analysis Type
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values will not be imputed; MMRM model is used on all available data assuming MAR (Assumes subjects with missing values behave the same as the observed data within that treatment group, i.e., the missingness is independent of unobserved data after accounting for the observed data in the model. ***Thus the dropouts or subjects with missing values may continue to benefit from the treatment as if they were still on treatment (just like completers.)***	Sensitivity (MMRM analysis assuming MAR)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	missing values imputed using MI assuming MNAR utilizing CCMV-4 missing value pattern (all available up to 4 monotone missing patterns) (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases up to 4 monotone missing patterns will be used in the imputation – see Section 3.4.1.3 for details. ***Thus this method relaxes the assumption of the primary analysis of using only completers to impute the missing data.***	Sensitivity (CCMV-4)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - include data after dropout	FAS	a range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant	Sensitivity (tipping point)
Difference in outcome improvement for all randomized subjects	- all randomized subjects regardless of what treatment subjects actually received - subjects who complete the study without missing efficacy assessments	FAS	subjects who completed all primary and secondary efficacy assessments without missing visits	Sensitivity (completer analysis)
Difference in outcome improvement for those who adhere to treatment	- subjects without major protocol violations that would impact efficacy assessments - include data after dropout	PP	missing values imputed using MI assuming MNAR utilizing CCMV missing value pattern (complete cases) (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.)***	sensitivity (PP analysis)
Difference in outcome improvement for those who adhere to treatment	- all randomized subjects; subject will be analyzed based on the actual treatment received - include data after dropout	FAS	missing values imputed using MI assuming MNAR utilizing CCMV missing value pattern (complete cases) (Assumes the probability of missing observations for any subject depends on the unobserved events. For the missing pattern, complete cases will be used in the imputation. ***Thus this method assumes dropouts or subjects with missing values have similar treatment effect as the completers within the respective treatment group.)***	sensitivity (as-treated analysis)

CCMV = complete case missing value; FAS = full analysis set; MI = multiple imputation; MAR = missing at random; MMRM = mixed effect model with repeated measurement; MNAR = missing not at random; PP = per-protocol analysis set; WASO2H = wake after sleep onset in the second half of the night

3.4 Efficacy/Pharmacodynamic Analyses

Unless specified otherwise, all efficacy endpoints will be summarized and analyzed using FAS. Baseline values for each efficacy parameter are defined in Section 6.2.

Unless specified otherwise, all efficacy/pharmacodynamic endpoints will be derived by calculating the averages of pairs of values [eg, average of LPS on Day 1 and Day 2 (denoted as Days 1/2 hereafter), average of LPS on Day 29 and Day 30 (denoted as Days 29/30 hereafter), …, etc.]

The primary and key secondary endpoints comparisons are tested following the gate-keeping testing procedure described in Section 3.3.3, Multiple Comparison/Multiplicity, to control for the overall type I error at the 0.05 significance level. The first primary efficacy endpoint comparison will be performed at the 0.05 significance level. The subsequent testing will only proceed if the previous test is statistically significant at the 0.05 level.

3.4.1 Primary Analyses

3.4.1.1 Primary Analysis

The primary efficacy endpoint is the change from baseline of LPS on Days 29/30 of LEM10 and LEM5 compared to PBO.

The null hypothesis of primary objective is that no difference exists in the mean change from baseline of LPS of Days 29/30 for treatment with LEM10 (or LEM5) as compared with PBO, and the corresponding alternative hypothesis is that a difference exists in the mean change from baseline of LPS of Days 29/30 for LEM10 (or LEM5) compared to PBO. The change from baseline of LPS on Days 1/2 and Days 29/30, will be analyzed using the mixed effect model repeated measurement analysis (MMRM) with factors of age group (55 to 64, and ≥ 65 years old), region (North America and Europe), treatment, visit (Days 1/2 and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline LPS as a covariate based on FAS. Since LPS is known to be non-normally distributed, a log-transformation will be used in the analysis. The unstructured covariance matrix (UN) will be used in the analysis. In the case of non-convergence of UN, the autoregressive [AR(1)] covariance matrix will be used in the model. Before the implementation of the MMRM model, the missing values will be imputed using pattern-mixture model multiple imputation (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed primary efficacy assessments without missing values). The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided.

MULTIPLE IMPUTATION

Step 1 (imputing missing data): Thirty multiple imputed complete datasets were to be constructed using the imputation regression model of age, sex, race (white, black, and other), and region (North America, and Europe), baseline BMI, baseline log(LPS), baseline ISI, baseline sSOL, and individual log(LPS) assessments on Days 1, 2 , 29, and 30, with a predefined arbitrary seed number (seed=2359). SAS PROC MI will be used to implement the imputation procedure using all available values. The dataset will be converted into monotone missing pattern by imputing arbitrary missing data as the first step. The monotone data will then be imputed with monotone regression method and MNAR. The sample SAS statement can be found in Section 7.

Step 2 (performing MMRM using each imputed dataset): The MMRM model with factors of age group (55 to 64, and ≥ 65 years old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline log(LPS) as a covariate will be applied to each imputed dataset. SAS PROC MIXED will be used for the MMRM analysis. The sample SAS statement can be found in Section 7.

Step 3 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 30 multiple imputed datasets from Step 2 will be combined using SAS PROC MIANALYZE to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules (Rubin DB, 1987). The sample SAS statement can be found in Section 7.

3.4.1.2 Subgroup Analyses

The primary endpoint described in Section 3.4.1 will be summarized using descriptive statistics by each subgroup listed below. The MMRM model assuming MAR will be applied to provide the LS means and 95% CI for the treatment difference. No hypothesis testing (p-value) will be performed in the subgroup analyses.

In addition, forest plot, and median and median change over time of LPS will also be provided for each subgroup listed below.

- Age group (55 to 64, 65 to 74, ≥75 years old)
- Sex (male and female)
- Race (white, black, Asian and other)
- Region (North America and Europe)
- BMI group (<18.5, 18.5 to <25, 25 to 30, >30)

3.4.1.3 Sensitivity Analyses

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described in Section 3.4.1 (MMRM analysis with MI for missing value imputation) will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described in Section 3.4.1 (MMRM analysis without missing value imputation) will be repeated on subjects who completed all primary efficacy assessments and have no missing visits.
- As-treated analysis: The same primary efficacy analyses described in Section 3.4.1 (MMRM analysis with MI for missing value imputation) will be repeated based on the actual treatment the subject received regardless of randomization.
- MMRM analysis assuming MAR: The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are missing at random (MAR; MMRM analysis without missing value imputation).
- MI Imputation assuming MNAR utilizing CCMV-4: The same MMRM method used in the primary analysis will be applied utilizing CCMV-4 (ie, up to 4 monotone missing patterns will be used for missing value imputation as follows):

Study days where results are available	**1**	**2**	**29**	**30**
Pattern 1	x	x	x	x
Pattern 2	x	x	x	.
Pattern 3	x	x	.	.
Pattern 4	x	.	.	.
x = result present; . = result missing				

- Tipping point analysis: A range of shifts will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant.

3.4.2 Secondary Analyses

3.4.2.1 Key Secondary Analyses

CHANGE FROM BASELINE OF SE ON DAYS 29/30

The change from baseline of SE on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64, and ≥65 year old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline SE as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 3.4.1. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline SE, baseline ISI, baseline sSE, and individual SE assessments on Days 1, 2 , 29, and 30.

CHANGE FROM BASELINE OF WASO2H ON DAYS 29/30

The change from baseline of WASO2H on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64 years, and ≥ 65 year old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO2H as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) covariance matrix will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 3.4.1. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline WASO2H, baseline ISI, baseline sWASO, and individual WASO2H assessments on Days 1, 2 , 29, and 30.

CHANGE FROM BASELINE OF WASO ON DAYS 29/30

The change from baseline of WASO on Days 1/2 and on Days 29/30 will be analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to 64, and ≥65 year old), region (North America, and Europe), treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effect, and the baseline WASO as covariates based on FAS. The unstructured covariance matrix will be used in the analysis. In case of non-convergence, the AR(1) covariance matrix will be used in the model. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data.

The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) of the treatment differences will also be provided.

Multiple Imputation

The same 3 steps (imputing missing data, performing MMRM using each imputed dataset, and combine results) will be implemented as described in Section 3.4.1, Primary Analyses. The complete data sets will be constructed using regression model of age, sex, race (white, black, and other), region, baseline BMI, baseline WASO, baseline ISI, baseline WASO, and individual WASO assessments on Days 1, 2 , 29, and 30.

The subgroup analyses including plots (forest plot, and mean and mean change from baseline over time) described in Section 3.4.1.2 and the sensitivity analyses described in Section 3.4.1.3 will be repeated for all key secondary endpoints.

3.4.2.2 Other Secondary Analyses

Unless it is covered from the same model from the primary and secondary efficacy endpoints, or specified otherwise, for all other secondary endpoints, the change from baseline assessments will be analyzed using MMRM assuming MAR (no missing value imputation) and the portion of responders will be analyzed using the Cochran Mantel Haenszel (CMH) test adjusted for age group. Missing values will be considered as non-responders in all responder analyses. No multiplicity adjustment will be made for all analyses.

POLYSOMNOGRAPHY

The following endpoints will be analyzed from PSG:

- Change from baseline of LPS, SE, WASO on Days 1/2 of LEM5 and LEM10 compared to PBO
- Change from baseline of LPS, SE, WASO on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of WASO2H on Days 1/2 of LEM5 and LEM10 compared to ZOL
- Change from baseline of WASO2H on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to PBO
- Change from baseline of WASO on Days 1/2 of LEM5 and LEM10 compared to PBO
- Change from baseline of WASO on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL
- Change from baseline of TST on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL and PBO
- Proportion of responders on Days 1/2 and Days 29/30 of LEM5 and LEM10 compared to ZOL and PBO in which the responder is defined as follows:

- Objective sleep onset responder: defined as LPS ≤20 minutes provided baseline LPS >30 minutes
- Objective sleep maintenance responder: defined as WASO ≤60 minutes, a reduction from baseline by >10 minutes provided baseline WASO >60 minutes

ELECTRONIC SLEEP DIARY

The following endpoints will be analyzed from the Sleep Diary:

- Change from baseline of mean sSOL, sWASO, sTST, and sSE over the first 7 and last 7 nights of the treatment period of LEM 5 and LEM 10 compared to ZOL and PBO. The derivation of sSOL, sWASO, sTST and sSE is detailed in Appendix 2.
- Proportion of responders over the first 7 and last 7 nights of the treatment period of LEM5 and LEM10 compared to ZOL and PBO in which the responder is defined as follows:
  - Subjective sleep onset responder: defined as sSOL ≤20 minutes and baseline sSOL >30 minutes
  - Subjective sleep maintenance responder: defined as sWASO ≤60 minutes, reduction from baseline by > 10 minutes, and baseline sWASO >60 minutes

POSTURAL STABILITY USING THE CDR POSTURE ASSESSMENT

- Change from baseline of units of body sway on Days 2/3 of the Treatment Period compared to ZOL

INSOMNIA SEVERITY INDEX AND FATIGUE SEVERITY SCALE

The following endpoints will be analyzed from the ISI and FSS:

- Change from baseline of the total score from items 1-7 as well as items 4-7 on the ISI at Day 31 of LEM5 and LEM10 compared to ZOL and PBO
- Change from baseline on the FSS score at Day 31 of LEM5 and LEM10 compared to ZOL and PBO

COGNITIVE PERFORMANCE ASSESSMENT BATTERY

The following endpoints will be analyzed from computerized performance assessment battery (PAB)

- Change from baseline of the 4 composite domain factor scores of PAB (power of attention, mean continuity of attention, mean quality of memory, and mean speed of memory retrieval) on Days 2/3

3.4.3 Other Efficacy/Pharmacodynamic Analyses

The following endpoints are considered exploratory. Comparison of LEM10 and LEM5 will be made with ZOL and PBO.

Unless specified otherwise, for all other efficacy analyses endpoints, the change from baseline assessment will be analyzed using MMRM assuming MAR and the portion of responders will be analyzed using the Cochran Mantel Haenszel test adjusted for age group. Missing values will be considered as non-responders in all responder analyses. No multiplicity adjustment will be made for all analyses.

POLYSOMNOGRAPHY

- Change from baseline of total duration (in minutes) of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM on Days 1/2 and Days 29/30
- Percentage of the change from baseline of total duration of sleep stage of non-REM (N1, N2, N3 separately and combined) and REM
    - per time in bed (TIB) on Days 1/2 and Days 29/30
    - per TST on Days 1/2 and Days 29/30
- Change from baseline of REM latency (defined as the first sleep epoch to first REM sleep epoch) on Days 1/2 and Days 29/30
- The change from baseline of mean REM latency will be analyzed separately for Days 1/2 and for Days 29/30 using Wilcoxon rank sum test. The treatment difference will be estimated using Hodges-Lehmann estimation, and the asymptotic (Moses) 95% CI for the difference will be provided.
- Change from baseline in number of awakenings on Days 1/2 and Days 29/30
- Change from baseline in number of long awakenings (defined as awakenings of 5 minutes or longer) on Days 1/2 and Days 29/30

ELECTRONIC SLEEP DIARY

- Change from baseline of the mean rating on the Quality of Sleep question from the Sleep Diary of the first 7 days and last 7 days of the Treatment Period
- Rebound insomnia endpoints during the Follow-up Period. Rebound insomnia is defined as worsened sleep (ie, higher value of sSOL or sWASO) relative to Screening after study drug treatment is completed.
    - Change from baseline of sSOL on each of the first 3 nights, mean of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
    - Change from baseline of sWASO on each of the first 3 nights, mean of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period

- Proportion of subjects whose sSOL is longer than at Screening at the following time points of the Follow-up Period by at least 5 minutes: each of the first 3 nights, mean of the first 3 night, mean of the first 7 nights, and mean of the second 7 nights
- Proportion of subjects whose sWASO is higher than at Screening at the following time points of the Follow-up Period by at least 5 minutes: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, and mean of the second 7

The actual value of sSOL and sWASO will be analyzed separately using analysis of covariance model (ANCOVA) with factors of age group (55 to <65, and ≥65 years older), region (North America, and Europe), and treatment for each time point (baseline, each of the first 3 night, mean of the first 3 nights, mean of the first 7 days, and mean of the last 7 days). The 95% CI of the treatment difference will be constructed for each time point. It will be considered as having strong evidence of rebound insomnia if the lower bound of the 95% CI of sSOL or sWASO for each of the 3 night, the mean of the first 3 nights, mean of the first 7 days, and mean of the second 7 nights of the Follow-up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested.

- Mean rating on morning sleepiness over the first 7 mornings and last 7 mornings of the Treatment Period and over the first 7 mornings and last 7 mornings of the Follow-up Period.

MORNING SLEEPINESS QUESTIONNAIRE

- Change from baseline of morning sleepiness ratings on Days2/3, and Days 30/31

POSTURAL STABILITY USING THE CDR POSTURE ASSESSMENT

- Change from baseline of units of body sway on Days 2/3 of the Treatment Period compared to PBO and on Days 30/31 of the Treatment Period compared to ZOL and PBO

COGNITIVE PERFORMANCE ASSESSMENT BATTERY

- Change from baseline of power of attention, continuity of attention, quality of memory, and speed of memory retrieval on Days 30/31

OTHER POLYSOMONGRAPHY ASSESSMENTS

The following endpoints from PSG will also be summarized using frequency count or descriptive statistics by treatment groups for exploratory purpose. No hypothesis testing will be performed on these endpoints.

Unless specified otherwise, the following endpoints will be summarized for Days 1/2 and Days 29/30:

- WASO1H

- Number of awakenings after persistent sleep
- Number and duration of long awakenings after persistent sleep
- Minutes of sleep stages: WASO, non-REM (N1,N2, N3 separately and combined), REM
- Percentage of minutes for each sleep stages per TIB: total wake time, non-REM (N1, N2, N3 separately and combined), REM
- Percentage of minutes for each sleep stages per TST: non-REM (N1, N2, N3 separately and combined), REM
- REM latency (defined as the first sleep epoch to first REM sleep epoch)
- Number of subjects with REM latency within 15 minutes of sleep onset
- WASO by quarter (every 2 hours) of the night

3.5 Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses

3.5.1 Pharmacokinetic Analyses

The plasma concentrations of lemborexant and its metabolites M4, M9, and M10, as well as zolpidem (where quantified) will be summarized using descriptive statistics by dose, time and day based on Safety Analysis Set.

A separate analysis plan for the population PK analyses will be developed and finalized before the database lock.

3.5.2 Pharmacokinetic/Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

A separate analysis plan for the PK/PD analyses will be developed and finalized before the database lock.

3.6 Safety Analyses

All safety analyses will be performed based on observed data using the Safety Analysis Set. Safety data will be summarized on an “as treated” basis using descriptive statistics or frequency count only. No hypothesis testing will be performed for safety analyses.

3.6.1 Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized using descriptive statistics by treatment group. Duration of exposure of study drug will be defined as the number of days between the date the subject received the first dose of study drug during Treatment Period and the date the subject received the last dose of study drug during Treatment Period, inclusive.

3.6.2 Adverse Events

The adverse event (AE) verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 20.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period), having been absent at pretreatment (before the Run-In Period) or

- Reemerges during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period), having been present at pretreatment (before the Run-In Period) but stopped before the last dose of study drug plus 14 days, or
- Worsens in severity during treatment (including the Run-In Period up to 14 days after the last dose of study drug from the Treatment Period) relative to the pretreatment state, when the AE is continuous.

For TEAEs occurred during the Run-in Period, the incidence of TEAEs will be summarized by SOC and PT.

An overview table of TEAE occurred during Treatment Period, including number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), deaths, severe TEAEs, study drug related TEAEs, TEAEs leading to study drug withdrawal during the Treatment Period will be provided. In addition, the following summaries will be produced for the TEAEs occurred during the Treatment Period:

- Incidence of TEAEs by PT in descending order
- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and severity
- Incidence of treatment-related TEAEs by SOC, PT, and severity
- Incidence of TEAEs by SOC, PT, and relationship to treatment
- Incidence of non-serious TEAEs (>5%) by SOC and PT

If a subject experiences more than one TEAE within a preferred term, the subject will be counted only once in the calculation of incidence of TEAE within that preferred term. Similarly, if a subject experiences more than one TEAE within a SOC, the subject will be counted only once in the calculation of incidence of TEAE within that SOC. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence with the highest severity will be used in the calculation of the incidence of TEAE within that preferred term (SOC) by severity. If a subject experiences more than one TEAE within a preferred term (or SOC), the occurrence considered most closely related to study drug will be used in

the calculation of the incidence of TEAE with that preferred term (SOC) by relationship (given by investigator).

The following summaries will also be presented for the treatment-emergent SAEs occurred during the Treatment Period:

- Incidence of treatment-emergent SAEs by SOC and PT
- Incidence of treatment-emergent SAEs by SOC, PT, and relationship to treatment.

In addition, number and percentage of subjects with TEAEs and treatment-related TEAEs leading to discontinuation from study treatment during the Treatment Period will also be summarized by MedDRA SOC, PT for each treatment group.

3.6.2.1 Selected Adverse Events

The following significant AEs will be summarized by SOC and PT:

- Cataplexy
- Falls
- Seizures
- Abuse liability events

Cataplexy includes the TEAEs with MedDRA PT of cataplexy, and drop attack.

Falls includes the TEAEs with MedDRA PT of "fall" only.

Seizure includes TEAEs with MedDRA PTs belonging to MedDRA Standardized MedDRA Query (SMQ) of "Convulsions" (Narrow Terms).

Abuse liability events includes TEAEs with MedDRA PT listed in Appendix 3.

3.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. With the exception of urinalysis, all quantitative parameters listed in protocol Section 9.5.1.5.5 Laboratory Measurements, the actual value and the change from baseline will be summarized at each visit using descriptive statistics by treatment group. For urinalysis, the actual and the change from baseline of pH and specific gravity will be summarized at each visit by treatment group. Analysis of changes from baseline 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. Shifts from baseline (LNH) to the Day 31, End of Treatment and the EOS visit will be provided by treatment groups for each laboratory parameter.

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

3.6.4 Vital Signs

For each vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, the actual value and changes from Study Baseline will be summarized by treatment group at each visit using descriptive statistics. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

In addition, clinically notable vital sign values will be identified using the criteria in Table 2. The clinically notable vital sign values will be summarized using frequency count at each visit by treatment group.

Table 2 Vital Sign Criteria

	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L
Weight	--	Increase of ≥7%	H
	--	Decrease of ≥7%	L
Respiratory Rate	>20 bpm	--	H
	< 10 bpm	--	L

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

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

3.6.5 Electrocardiograms

For each ECG parameters (including PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval and heart rate) and actual value and changes from baseline will be summarized by treatment group at each visit using descriptive statistics. Shift tables from

baseline to the Day 31, End of Treatment and the EOS visits will be presented by treatment group for ECG interpretation (categorized as normal and abnormal).

In addition, maximum postbaseline measurement will also be tabulated by treatment group as follows:

- Number and percentage of subjects with QTcF of >450 msec, and >500 msec during the treatment
- Number and percentage of subjects with a QTcF increment of >30 msec, and >60 msec from the baseline visit.
- Number and percentage of subjects with PR of >220 msec
- Number and percentage of subjects with QRS of >120 msec

3.6.6 Other Safety Analyses

3.6.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed using a self-rated electronic version of the C-SSRS (eC-SSRS). The eC-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. The incidence of suicidal ideation, suicidal behavior, and self-injurious non-suicidal behavior at each visit will be summarized by treatment group using frequency count. A subject will be counted once in a category if at least one question is answered positive in the category.

3.6.6.2 Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ)

Withdrawal symptoms will be assessed using the T-BWSQ at the EOS visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score = 0), "Yes – moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses will be the subject's total score. The total score will be summarized by treatment group using descriptive statistics. In addition, the number and percentage of subjects with a total score of ≥3 will be summarized using frequency count.

3.7 Other Analyses

3.7.1 Health Outcome Economics Analyses

3.7.1.1 EQ-5D-3L

The EQ-5D-3L instrument comprises questions on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue score (EQ VAS). Each dimension has 3 levels: no problem, some problems, extreme problems and the EQ VAS is ranged from 0 ("Worst imaginable health state") to 100 ("Best imaginable health

state"). Each dimension score will be summarized separately at Baseline and Day 31 using frequency count on observed data only with no imputation. The change from baseline of EQ VAS will be analyzed using ANCOVA with factors of age group (55 to 64, and ≥65 years old), region (North America, and Europe), treatment based on FAS and baseline VAS as a covariate.

3.7.1.2 Patient Global Impression (PGI) - Insomnia

The PGI-Insomnia questionnaire captures the global impression of the study medication's effect at the end of treatment and is collected on Day 31 visit only. The PGI-Insomnia has 3 items related to study medication effect (helped/worsened sleep, decreased/increased time to fall asleep, and increased/decreased TST) on a 3-point scale (1=positive medication effect, 2=neutral medication effect, and 3=negative medication effect) and 1 item related to perceived appropriateness of study mediation strength also on a 3-point scale (medication: 1=too strong, 2=just right, and 3=too weak). Each item will be analyzed summarized separately ("positive medication effect" versus others for the first 3 item; "just right" versus others for the last item) using chi-square test on observed data only based on FAS with no imputation for missing values, and repeated for age subgroups.

3.8 Exploratory Analyses

None

4 INTERIM ANALYSES

An interim analysis is planned to be conducted after approximately 50% of subjects (approximately n=475 subjects) have been randomized and either completed Day 31 assessments or discontinued from the study. This interim analysis will be conducted for administrative reasons as detailed in the separate Interim Analysis Charter. When the specified number of subjects has completed the Day 31 assessments, an independent statistician external to the Sponsor will be provided with the relevant PSG dataset and will be unblinded to the primary endpoint, ie, change from baseline in WASO2H for the mean of Days 29 and 30. A conditional power will be calculated to predict the probability that the trial will achieve a significant treatment effect for WASO2H in the LEM10 versus ZOL arms at the end of the study, given what is observed at the time of interim analysis. The interim analysis will be limited to the comparison of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30. No other endpoints, dose groups, or timepoints will be analyzed at the interim analysis. The study will not be terminated for either futility or efficacy. Therefore no impact to the type I error rate is expected.

The method of calculating the conditional power will be detailed in the Interim Analysis Charter, along with operational procedures, unblinding procedures, procedures for communicating the results of the conditional power calculation and recipients of this information. To preclude potential influence on the conduct of the remainder of the study, disclosure of the interim results will be limited to a prespecified set of executive-level individuals at the sponsor and sponsor's co-development partner. No individuals involved

with the conduct of the study will have access to the interim data or the results of the interim analysis (i.e., the conditional power of LEM10 versus ZOL on the change from baseline in WASO2H for the mean of Days 29 and 30).

Enrollment of subjects will not be stopped during the interval during which the interim analysis is conducted. The interim analysis may be waived or otherwise not conducted, for reasons including but not limited to a higher than anticipated enrollment rate which would make the interim analysis unnecessary as the majority of subjects would have been enrolled by the time the interim analysis is concluded.

5 CHANGES IN THE PLANNED ANALYSES

The following changes were made in version 2.0 of the SAP from version 1.0:

- Section 3.3.5 “Handling of Missing Data, Dropouts, and Outlier”, Section 3.3.6 “Other Considerations”, Section 3.4 “Efficacy/Pharmacodynamic Analyses”: Sensitivity analyses are added to evaluate different missing value patterns. Sensitivity and subgroup analyses are added to key secondary efficacy endpoints for completeness.
- Section 3.6.2.1 “Selected Adverse Events” and Appendix 13.3 “List of Abuse Liability Events”: The definition of “Abuse Lability Events” is updated to utilize MedDRA SMQs. Appendix 13.3 from version 1.0 is removed from this section.
- Section 6.1 “Visit Window”: Visit window description is added for diary efficacy endpoints.
- Throughout the document: Editorial comments are made to correct typos or for clarification purposes.

The following changes were made in version 3.0 of the SAP from version 2.0:

- Section 3.1.2“Secondary Endpoints”, Section 3.3.3 “Multiple Comparisons/Multiplicity”: The order of the objectives and endpoints is updated to incorporate feedback from regulatory authorities.
- Section 3.2.1 “Definitions of Analysis Sets”: List of exclusion reasons from the PP population is updated.
- Section 3.6.2.1 “Selected Adverse Events” and Appendix 3 “List of Abuse Liability Events”: The definition of “Abuse Lability Events” is updated to revert back to the approach from version 1.0.
- Section 7 “Programming Specifications”: The description of a planned tipping point analysis has been included.
- Throughout the document: Editorial comments are made to correct typos or for clarification purposes.

6 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

6.1 Visit Window

Study Day 1 is defined as the date of the first dose of study drug during the Treatment Period. The nominal visit (ie, study visit captured on the CRF) will be used as the analysis visits in all by-visit summaries except for sleep diary efficacy endpoints. The Early Term visit will be considered as unscheduled visit and will not be included in the by-visit summary. Where applicable, the Early Term visit will be used along with the Day 31 visit for completers as the End of Treatment visit for the safety analyses.

For diary efficacy endpoints, the following visit window will be applied:

Timepoint	Visit Window (in study days)
First 7 days of Treatment	2-8
Last 7 days of Treatment	22-36[a]

a: Last seven days within this window while on treatment

6.2 Baseline Assessment

Unless otherwise specified, baseline measurement is the last observed measurement, including unscheduled assessments, prior to the first dose of study medication of treatment period for a given assessment. For the following endpoints, baseline measurement is defined as follows:

- PSG parameters : average of the two PSG recordings during the Run-in Period
- Sleep diary parameters:
  - For rebound insomnia: the mean of diary data entered on the last 7 mornings before the Screening PSG during the Screening Period
  - Other Sleep Diary-derived endpoints: the mean of diary data entered on the last 7 mornings before the first Baseline PSG during the Run-In Period
- Morning sleepiness questionnaire at 1.5 hours after wake time on mornings after PSG recordings: Average of the 2 morning sleepiness ratings during the Run-in Period
- ISI: Last available ISI measurement on or prior to Visit 3
- Postural Stability parameters: Average of non-missing measurements from Visit 3 Visit 4
- Cognitive PAB parameters: Average of non-missing measurements from Visit 3 and Visit 4
- FSS: Last available FSS measurement on or prior to Visit 5
- EQ-5D-3L: Last available EQ-5D-3L measurement on or prior to Visit 5
- C-SSRS: Visit 5 (“since last visit” form)

6.3 Missing Data Handling

Unless stated otherwise, missing values will be considered as non-responders in responder analyses and the continuous variables will be analyzed using MMRM to handle the missing values assuming MAR in all other efficacy analyses. Details can be found in Section 3.4

All safety analyses will be performed based on the observed data only.

6.3.1 Polysomnography, Cognitive Performance Assessment, Posture Stability, and Morning Sleepiness Questionnaire

Each PSG, PAB, posture stability, and morning sleepiness questionnaire parameters will be derived by calculating the averages of pairs of values, i.e., the average of the two PSG recordings during the Run-in Period, Day 1 and Day 2, and Day 29 and Day 30. If one of each pair of values is missing, the other available value will be taken as the average of the pair; if both values are missing, then the parameter will be missing for the corresponding pair.

6.3.2 Sleep Diary

Each Sleep Diary parameter will be derived by calculating the average of weekly (7 days) diary parameter values. For the follow-up period, if the first 7 nights overlaps with the last 7 nights (eg, the follow-up period is less than 14 days in total), the last non-overlaps nights will be used in calculating the average value for the last 7 nights.

For each Sleep Diary parameter at baseline, if no more than 2 of the 7 nights' values are missing, the available values will be used to calculate the mean. If more than 2 values are missing, the parameter will be considered missing for baseline. For each Sleep Diary parameter during treatment period and follow-up period, if at least 4 of the 7 nights' values are available, the available values will be used to calculate the mean. If less than 4 values are available, the parameter will be considered missing for the corresponding time point.

7 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

The following sample SAS statement provides the framework for the MI method:

CONVERT DATASET INTO MONOTONE MISSING DATA PATTERN (IMPUTING ARBITRARY MISSING DATA):

```
PROC MI data=<dataset> nimpute=30 seed=2359 out=<dataset1>;
  VAR age BMI baseline… visit1-visit4;
  MCMC chain=multiple nbiter=500 niter=300 impute=monotone;
  BY treatment;
RUN;
```

IMPUTE MISSING VALUES:

```
PROC MI data=<dataset1> nimpute=1 seed=2359 out=<dataset2>;
  CLASS treatment sex race region;
  MONOTONE regression ( /details);
  MNAR model (visit1-visit4/ modelobs=CCMV);
  VAR treatment age sex race region BMI baseline….;
  BY _imputation_;
RUN;
```

PERFORMING MMRM:

```
PROC MIXED data=<dataset2>;
  CLASS subject treatment agegrp visit;
  MODEL value=treatment agegrp region visit visit*treatment / ddfm=kr;
  REPEAT visit/sub=subject type=UN group=treatment;
  LSMEANS visit*treatment;
  ESTIMATE '5mg  –  ZOL Days 1_2'     treatment 0 -1 1 0  visit*treatment   0 0 -1 0 1 0 0 0/CL;
  ESTIMATE '10mg – ZOL Days 1_2'      treatment 0 -1 0 1  visit*treatment   0 0 -1 0 0 0 1 0/CL;
  ESTIMATE '5mg  –  ZOL Days 29_30'   treatment 0 -1 1 0  visit*treatment   0 0 0 -1 0 1 0 0/CL;
  ESTIMATE '10mg – ZOL Days 29_30'    treatment 0 -1 0 1  visit*treatment   0 0 0 -1 0 0 0 1/CL;
  BY _imputation_;
  ODS output estimates=<dataset3>;
RUN;
```

COMBINE RESULTS:

```
PROC MIANALYZE data=<dataset3>;
  MODELEFFECTS estimate;
  STDERR stderr;
RUN;
```

VARIABLE ORDER TO BE USED IN THE PROC MI PROCEDURES:

To Create Monotone Missing Data Pattern

- LPS: age, baseline BMI, baseline ISI, baseline log(sSOL), baseline log(LPS), log(LPS) at Day1, log(LPS) at Day2, log(LPS) at Day29, log(LPS) at Day30
- SE: age, baseline BMI, baseline ISI, baseline sSE, baseline SE, SE at Day1, SE at Day2, SE at Day29, SE at Day30
- WASO2H: age, baseline BMI, baseline ISI, baseline sWASO, baseline WASO2H, WASO2H at Day1, WASO2H at Day2, WASO2H at Day29, WASO2H at Day30
- WASO: age, baseline BMI, baseline ISI, baseline sWASO, baseline WASO, WASO at Day1, WASO at Day2, WASO at Day29, WASO at Day30

To Impute Missing Values

- LPS: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline log(sSOL), baseline log(LPS), log(LPS) at Day1, log(LPS) at Day2, log(LPS) at Day29, log(LPS) at Day30
- SE: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sSE, baseline SE, SE at Day1, SE at Day2, SE at Day29, SE at Day30
- WASO2H: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sWASO, baseline WASO2H, WASO2H at Day1, WASO2H at Day2, WASO2H at Day29, WASO2H at Day30
- WASO: treatment, age, sex, race, region, baseline BMI, baseline ISI, baseline sWASO, baseline WASO, WASO at Day1, WASO at Day2, WASO at Day29, WASO at Day30

TIPPING POINT SENSITIVITY ANALYSIS:

The following sample SAS statements and algorithm provide the framework for the Tipping Point Sensitivity Analysis:

A tipping point sensitivity analysis will be conducted on the endpoints LPS (Log LPS), SE, WASO and WASO2H using the multiple imputation methodology as described in the section above but with the following modifications:

1. The second MI procedure (monotone missing values) is to be modified to introduce an adjustable shift (i.e sensitivity parameter) to the imputed values for only the treatment groups LEM10 and LEM5, corresponding to a MAR assumption when the shift is zero. These shifts are to be applied to Day29 and Day30 only.

```
PROC MI data=<dataset1> nimpute=1 seed=2359 out=<dataset2>;
    CLASS treatment sex race region;
    MONOTONE regression ( /details);
    MNAR adjust (visit3/ shift=<shift> adjustobs=(treatment=LEM5));
    MNAR adjust (visit4/ shift=<shift> adjustobs=(treatment= LEM5));
    MNAR adjust (visit3/ shift=<shift> adjustobs=(treatment=LEM10));
    MNAR adjust (visit4/ shift=<shift> adjustobs=(treatment= LEM10));
    VAR treatment age sex race region BMI baseline… V5 V6 V7 V8;
    BY _imputation_;
RUN;
```

2. If the MAR (shift=0) model has a p-value that is significant (<0.05), then the <shift> value will be systematically incremented until the resulting p-value is >=0.05.
3. Step 2 may be repeated iteratively starting with the shift found just prior to p-value >0.05 ending with the p-value>=0.05 found in Step 2, using smaller increments, until a shift is found where the rounded p-value has a value of 0.05 to a reasonable accuracy.
4. The values for <shift> in Step 1 will be applied uniformly (same shift) to both LEM 5mg and LEM 10gm at both Day29 and Day 30.

5. The values for <shift> will correspond to worsening values for the endpoint according to the following:

- Increasing positive shift values (LPS, WASO, WASO2H)
- Increasing negative shift values (SE)

6. The following specifies which comparisons are of interest when evaluating p-values for this procedure:

- LEM 5mg and LEM10mg vs. Placebo (LPS, SE, WASO)
- LEM 5mg and LEM 10mg vs. Zolpidem (WASO2H)

8 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.4 (or later versions). In the event that certain features graphical analyses cannot be implemented by SAS, other statistical software such as Splus can be employed.

The conditional power calculated for the interim analysis will be performed using EAST® version 6 (or later versions).

9 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings and graphs shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

10 REFERENCES

ICH Final Concept Paper E9(R1): Addendum to statistical principles for clinical trials on choosing appropriate estimands and defining sensitivity analyses in clinical trials dated 22October 2014.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharmaceutical Statistics 2012,11:456-461, 10 September 2012.

Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.

Appendix 1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

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

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Derivations of Efficacy Endpoints from Electronic Sleep Diary

The following 7 questions are captured in the electronic Sleep Diary:

Q1: What time did you try to go to sleep?

Q2: How long did it take you to fall asleep?

Q3: How many times did you wake up, not counting your final awakening?

Q4: In total, how long did these awakenings last?

Q5: What time was your final awakening?

Q6: After your last awakening, how much longer did you try to sleep?

Q7: What time did you get out of bed for the day?

The efficacy endpoints from electronic Sleep Diary are defined as follows:

- sSOL= Q2
- sWASO = Q4 + Q7 – Q5
- sTST = TIB – time spent awake [where TIB = Q7 – Q1; and time spent awake = Q2 + Q4 + Q7 – Q5]
- sSE = sTST/TIB (as defined above)

Appendix 3 List of Abuse Liability Events

Code	PT
10061422	Abnormal behaviour
10000125	Abnormal dreams
10063746	Accidental death
10000381	Accidental overdose
10000383	Accidental poisoning
10001022	Acute psychosis
10054196	Affect lability
10001443	Affective disorder
10001488	Aggression
10001497	Agitation
10001666	Alice in wonderland syndrome
10001854	Altered state of consciousness
10053549	Altered visual depth perception
10001949	Amnesia
10061423	Amnestic disorder
10002368	Anger
10002511	Anhedonia
10002711	Anterograde amnesia
10002820	Antisocial behaviour
10002855	Anxiety
10002942	Apathy
10003472	Asocial behaviour
10003739	Attention-seeking behaviour
10049848	Balance disorder
10004224	Belligerence
10005885	Blunted affect
10050012	Bradyphrenia
10057668	Cognitive disorder
10061046	Communication disorder
10010219	Compulsions
10010297	Confabulation
10067494	Confusional arousal
10010305	Confusional state

10050093	Consciousness fluctuating
10010947	Coordination abnormal
10012177	Deja vu
10012218	Delirium
10012239	Delusion
10012335	Dependence
10077805	Depersonalisation/derealisation disorder
10012374	Depressed mood
10012378	Depression
10012411	Derailment
10012422	Derealisation
10013142	Disinhibition
10013395	Disorientation
10013457	Dissociation
10013462	Dissociative disorder
10013468	Dissociative identity disorder
10013496	Disturbance in attention
10061108	Disturbance in social behaviour
10013573	Dizziness
10061111	Drug abuser
10013659	Drug administered at inappropriate site
10052237	Drug detoxification
10066053	Drug diversion
10052804	Drug tolerance
10052806	Drug tolerance increased
10079381	Drug use disorder
10013752	Drug withdrawal convulsions
10013753	Drug withdrawal headache
10013754	Drug withdrawal syndrome
10013887	Dysarthria
10054940	Dyslogia
10014551	Emotional disorder
10049119	Emotional distress
10048779	Energy increased
10015535	Euphoric mood
10070246	Executive dysfunction

10016256	Fatigue
10016275	Fear
10016322	Feeling abnormal
10016330	Feeling drunk
10016338	Feeling jittery
10016344	Feeling of despair
10016352	Feeling of relaxation
10016754	Flashback
10016759	Flat affect
10016777	Flight of ideas
10017062	Formication
10019063	Hallucination
10019070	Hallucination, auditory
10019072	Hallucination, olfactory
10062824	Hallucination, synaesthetic
10019074	Hallucination, tactile
10019075	Hallucination, visual
10019079	Hallucinations, mixed
10019133	Hangover
10020400	Hostility
10048533	Hypervigilance
10020937	Hypoaesthesia
10021212	Ideas of reference
10021402	Illogical thinking
10021403	Illusion
10049564	Impaired driving ability
10071176	Impaired reasoning
10049976	Impatience
10021567	Impulsive behaviour
10021588	Inappropriate affect
10021630	Incoherent
10021703	Indifference
10022523	Intentional overdose
10074903	Intentional product misuse
10023118	Jamais vu
10023236	Judgement impaired

10024264	Lethargy
10024825	Loose associations
10025429	Magical thinking
10026749	Mania
10027175	Memory impairment
10061284	Mental disorder
10027374	Mental impairment
10048294	Mental status changes
10027940	Mood altered
10027951	Mood swings
10028330	Muscle rigidity
10028747	Nasal necrosis
10028765	Nasal septum perforation
10028766	Nasal septum ulceration
10028896	Needle track marks
10061862	Neonatal complications of substance abuse
10029216	Nervousness
10029412	Nightmare
10033295	Overdose
10033664	Panic attack
10033670	Panic reaction
10033775	Paraesthesia
10033848	Paramnesia
10033864	Paranoia
10061910	Parasomnia
10063117	Paroxysmal perceptual alteration
10034719	Personality change
10061355	Poisoning
10067669	Prescription form tampering
10069330	Product tampering
10070592	Product used for unknown indication
10037211	Psychomotor hyperactivity
10037213	Psychomotor retardation
10049215	Psychomotor skills impaired
10061920	Psychotic disorder
10053632	Reactive psychosis

10038001	Rebound effect
10038743	Restlessness
10038965	Retrograde amnesia
10039897	Sedation
10040026	Sensory disturbance
10061567	Sensory level abnormal
10041052	Sluggishness
10041317	Somatic delusion
10062684	Somatic hallucination
10041349	Somnolence
10041953	Staring
10042264	Stupor
10067688	Substance abuser
10070964	Substance use
10079384	Substance use disorder
10072387	Substance-induced mood disorder
10072388	Substance-induced psychotic disorder
10042635	Suspiciousness
10043114	Tangentiality
10043431	Thinking abnormal
10043495	Thought blocking
10052214	Thought broadcasting
10043496	Thought insertion
10043497	Thought withdrawal
10070863	Toxicity to various agents
10044380	Transient global amnesia
10056326	Transient psychosis
10049414	Treatment noncompliance
10048010	Withdrawal syndrome
MedDRA 20.1	

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