16.1.1 Protocol and Protocol Amendments

The latest version of the study protocol and all previous versions are provided on the following pages:

- V4.0 01 Oct 2019 (Amendment 02)
- V3.0 03 Jun 2019 (Amendment 01)
- V2.0 12 Apr 2019 (revised original protocol)
- V1.0 12 Apr 2019 (original protocol)

REVISION HISTORY

Revisions to Version 3.0

New version /date: Version 4.0/01 Oct 2019 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Modified the Inclusionary Criteria to include subjects who meet both criteria for intermittent and frequent zolpidem (ZOL) use during 1 week each of the last 2 weeks of the 3-week Screening Period under Cohort 1	To facilitate the enrollment by including all appropriate subjects in cohort 1	Section 2 - Inclusion Criteria Section 2 – Study Design Section 9.1 Section 9.1.1.1 Section 9.3.1 Section 9.4.3
Simplified the Exclusion Criterion No. 12	For clarification	Section 2 - Exclusion Criteria Section 9.3.2
Provided description of physical examination	To clarify procedures for performing full physical examinations	Section 9.5.1.2.1
Added a word 'approximately' before the number of subjects	For clarification	Section 2 – Number of Subjects Section 2 – Sample Size Rationale Section 2 – Study Design Section 9.1 Section 9.1.1.1 Section 9.4.3 Section 9.7.2
Corrected the overall number of subjects received lemborexant (LEM)	For correction	Section 7.1.2.1
Modified footnote "i" in Table 3 and footnote "e" in Table 5	To clarify procedures for performing a physical examination	Table 3 footnote Table 5 footnote
Deleted the text regarding study-specific adverse events and added as 'not applicable'	For consistency with other Phase 3 protocols	Section 9.5.1.5.3 Section 9.5.4.3.2
Changed the Study Director and Medical Monitor to PPD	Administrative change	Protocol signature Page

Revisions to Version 2.0

New version /date: Version 3.0/03 Jun 2019 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Addition of actigraphy	To provide objective data on the effect of LEM and ZOL on sleep and wake parameters	Section 2 – Exploratory Objectives Section 2 – Study Design Section 2 – Efficacy Assessments (Core Study only) Section 2 – Statistical Methods Section 2 – Efficacy Analyses (Core Study only) Section 8.3 Section 9.1.1.1 Section 9.1.1.2 Section 9.1.2.1 Section 9.5.1.3.5 Section 9.7.1.1.3 Section 9.7.1.6.3 Table 3
Reorganization of secondary and exploratory objectives and endpoints	To focus secondary endpoints on successful transition due to dose-related aspects of LEM	Section 2 – Secondary Objectives Section 2 – Exploratory Objectives Section 8.2 Section 8.3 Section 9.7.1.1.2 Section 9.7.1.1.3 Section 9.7.1.6.2 Section 9.7.1.6.3
Clarification of cohort assignment based on ZOL use frequency	Clarification	Section 2 – Study Design Section 2 - Inclusion Criteria Section 2 - Exclusion Criteria Section 9.1 Section 9.1.1.1 Section 9.1.2.1 Section 9.3.1 Section 9.3.2 Section 9.4.3
Clarification of PK sampling in the event of an SAE or severe unexpected AE and its resolution	Clarification	Table 3 Table 5
Clarification of data collection at Visit 2a	Clarification	Table 3

Revisions to Version 1.0

New version /date: Version 2.0/12 Apr 2019

Change	Rationale	Affected Protocol Sections
Modified the text in Exclusion Criterion No. 1 to replace urine pregnancy test with serum pregnancy test.	Administrative change	Synopsis –Exclusion criteria Section 9.3.2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	E2006/Lemborexant
Indication:	Insomnia
Phase:	3b
	V1.0 12 Apr 2019 (original protocol)
	V2.0 12 Apr 2019 (revised original protocol)
	V3.0 03 Jun 2019 (Amendment 01)
	V4.0 01 Oct 2019 (Amendment 02)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Pilot Study to Evaluate Next-Dose Transition From Zolpidem to Lemborexant for the Treatment of Insomnia

Investigator(s)

Unknown

Sites

Approximately 15 sites within the United States of America

Study Period and Phase of Development

Phase 3b pilot study

Estimated duration of up to 38 weeks from first subject in to last subject's last visit.

Objectives

Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking zolpidem tartrate immediate release (ZOL-IR) or zolpidem tartrate extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

Secondary Objectives (revised per Amendment 01)

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking zolpidem (ZOL)

Exploratory Objectives (revised per Amendment 01)

- To evaluate LEM5 or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To compare nights on which an evening dose of LEM5 or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
  - Total Sleep Time (TST)
  - Sleep Efficiency (SE)
  - Wake After Sleep Onset (WASO)
  - Wake Bouts
- To compare the daytime after an evening dose of LEM5 or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
  - Sleep Bouts

Study Design

E2006-A001-312 is a multicenter Phase 3b pilot study evaluating the transition of LEM when

administered as a replacement for ZOL-IR or ZOL-ER.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. The Pretreatment and Treatment Phases will comprise the Core Study. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted.

Core Study

Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

Screening Period

During the Screening Period, subjects will be required to bring the container of their prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the frequency of ZOL is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing these data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days out of the allowable 21-day Screening Period in order to be eligible for study inclusion. Eligible subjects will also be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period. Subjects will be provided with a daily log (sleep log) to note the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log. (revised per Amendment 01)

Subjects will return to clinic at the end of the Screening Period. Actigraph data will be downloaded and transmitted to the central reader, along with the sleep log of bedtimes, morning wake times, and the approximate times when the actigraph was replaced on the subject's wrist. (revised per Amendment 01)

Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period, or (revised per Amendment 01)
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)
- The subjects who meet both criteria for intermittent and frequent ZOL use for 1 week each of the last 2 weeks of the 3-week Screening Period will be assigned to Cohort 1 and referred to as Cohort 1-Mixed. (revised per Amendment 02)

All subjects (approximately 20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (approximately 40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio. (revised per Amendment 02)

Baseline Period

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation, return their actigraphs and sleep logs to the study site, and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible will enter the Titration Period. (revised per Amendment 01)

Treatment Phase

Titration Period

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep at night. Subjects will continue to wear their actigraphs throughout the Titration Period, with the same instructions for use. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed. Subjects will be instructed to not alter (ie, break or cut) their tablets of LEM. (revised per Amendment 01)

Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will decide when to take LEM according to their usual pattern, with the requirement that they take LEM at least once per week during the 2-week Titration Period. (revised per Amendment 01)

Cohort 2 (Frequent Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

For subjects with a starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site should they feel that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.

For subjects with a starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site should they feel that LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of LEM dose change during the Core Study, the reason for the dose change will be recorded in the case report form (CRF). Subjects will be allowed 1 LEM dose adjustment during the Titration Period. Every morning, subjects will enter their insomnia drug use data into the data collection system and record their sleep log data, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each study visit except Follow-up Visit. (revised per Amendment 01)

Upon completion of the Titration Period, actigraphs will be returned to the study site, and subjects will be considered for eligibility to enter the Extension Phase. (revised per Amendment 01)

Extension Phase

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of LEM that they took at the end of the Titration Period. Subjects will subsequently return to clinic as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Treatment Phase for subjects not entering the Extension Phase or after the end of the Extension Phase, for subjects entering the Extension Phase).

End of Study

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

Number of Subjects

Approximately 110 subjects will be screened to provide approximately 60 subjects (approximately 20 subjects in Cohort 1 and approximately 40 subjects in Cohort 2 [approximately 20 subjects each in LEM5 and LEM10]). (revised per Amendment 02)

Inclusion Criteria

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) criteria for Insomnia Disorder, either currently or prior to ZOL use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of frequent or intermittent use of ZOL (based on review of drug use data).

- Frequent use is defined as taking ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period (revised per Amendment 02)
- Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period; or taking ZOL as per the intermittent criteria for 1 week of the last 2 weeks of the 3-week Screening Period, and taking ZOL as per the frequent criteria for 1 week of the last 2 weeks of the 3-week Screening Period (revised per Amendment 02)

6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

Exclusion Criteria

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

   NOTE: All females will be considered to be of childbearing potential unless they are

postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

3. Any history of moderate or severe obstructive sleep apnea (OSA)
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Drug use data do not confirm intermittent or frequent use as defined in the Inclusion Criterion No. 5 (revised per Amendment 02)
13. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
14. 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 (A list of prohibited concomitant medications is presented in the protocol).
15. Used any pharmacologic modality of treatment for insomnia other than zolpidem, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
16. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
17. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
18. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
19. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
20. Hypersensitivity to lemborexant or any of the excipients.
21. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
22. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during

the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety. 23. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years 24. History of drug or alcohol dependency or abuse within approximately the last 2 years 25. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent 26. Previously participated in any clinical trial of lemborexant
Study Treatment(s) **Core Study** **Test drug:** LEM5 or LEM10 taken orally in tablet form at night within a few minutes of the time the subject intends to sleep, according to the subject's predetermined intermittent or frequent use schedule. **Comparator Drug:** Not applicable *Extension Phase* **Test drug:** LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.
Duration of Treatment A maximum of 14 weeks: 2 weeks of LEM5 or LEM10 during the Treatment Phase of the Core Study, 12 weeks during the Extension Phase
Concomitant Drug/Therapy Prohibited medications should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Phase. Prohibited medications include moderate and strong cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers, and medications that have known sedating effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants). If a medication is not on the list of prohibited medications but in the opinion of the investigator causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study. Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study.
Assessments **Screening Assessments (Core Study only)**

Sleep Disorders Screening Battery (SDSB):
The SDSB will include:

- STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA
- IRLS: a subjective scale comprising 10 questions, which measures severity of symptoms of restless legs syndrome

Sleep Drug History Questionnaire
Subjects will be asked questions about their history and response to prior sleep medications.
Sleep Drug Experience Interview – Zolpidem
Subjects will be asked questions about their subjective experiences while taking ZOL at the end of the Screening Period.

Efficacy Assessments (Core Study only)

Patient Global Impression – Insomnia
The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep. The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening.
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. The ISI will be completed at each study visit except Follow-up Visit.
Quality of Sleep Rating
The Quality of Sleep Rating is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.
Sleep Drug Experience Interview – Lemborexant
Subjects will be asked questions about their subjective experiences while taking LEM at the end of the Titration Period.
Actigraphy (revised per Amendment 01)
An actigraph is a device that consists of a compact, wrist-worn, battery-operated activity monitor that looks like a wrist watch. This device incorporates a multidirectional accelerometer to monitor degree and intensity of motion. Data from an actigraph are collected at a sampling rate of every 30 seconds and are scored as sleep or wake with a validated algorithm. Sleep/wake parameters are calculated from the scored data. A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the subject. Actigraphy data will be used to evaluate the following sleep and wake parameters for subjects during the Screening and Titration Periods:

- TST: The total time spent in sleep according to the epoch-by-epoch wake/sleep categorization during time in bed (TIB)
- SE: 100% × the total duration of sleep epochs during the defined nocturnal sleep period/TIB
- WASO: The total time spent awake according to the epoch-by-epoch wake/sleep categorization

between sleep start (based on 'lights out') and 'got up'
- Wake Bouts: Wake of ≥ 5 minutes that occur during TIB
- Sleep Bouts: Continuous sleep ≥ 10 minutes that occur during Time Out of Bed (TOB)

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments (Core Study and Extension Phase)

Safety assessments will consist of monitoring and recording all adverse events (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. Subjects will be asked about falls at every visit.

Adjudication Committee

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

Columbia – Suicide Severity Rating Scale

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

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 consecutive months as designated in the Schedule of Procedures/Assessments.

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments. This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, PCP, opiates, benzodiazepines, barbiturates, and amphetamines.

Bioanalytical Methods

Not applicable.

Statistical Methods

The study endpoints for efficacy and safety will be presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed.

Primary Endpoint

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses, or preference to continue insomnia management with another health care provider).

Secondary Endpoints (revised per Amendment 01)

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

Exploratory Endpoints (revised per Amendment 01)

The exploratory endpoints are as follows:

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.
- To compare nights on which an evening dose of LEM5 or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- To compare the daytime after an evening dose of LEM5 or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Mean Duration of Sleep Bouts

Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the Full Analysis Set.

Efficacy Analyses (Core Study only)

All efficacy analyses will be conducted on the FAS.

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.
- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall,
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of the Titration Period dose groups.
- Average value of following sleep-related actigraphy variables will be summarized by treatment over the nights on which an evening dose of LEM5, LEM10, and ZOL was taken. (revised per Amendment 01)
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- Average value of wake-related actigraphy variable, mean duration of Sleep Bouts will be summarized by treatment over the daytime after an evening dose of LEM5, LEM10, and ZOL was taken. (revised per Amendment 01)

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses (Core Study and Extension Phase)

Evaluations of safety data will be performed on the SAS.
The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized for Cohort 1 (Intermittent ZOL use) and

Cohort 2 (Frequent ZOL use) using descriptive statistics using end of titration dose group. AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.
Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and PTs related to drug abuse liability, will be summarized separately. The results of the deliberation of the Adjudication Committee will be reported separately. In addition, 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, as per the Adjudication Committee description.

Other Analyses (Core Study)

Efficacy endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan. (revised per Amendment 01)

Interim Analyses

No interim analyses are planned for this study.

Sample Size Rationale

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll approximately 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for zolpidem. Approximately 20 subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and approximately 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use). This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to evaluate whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BMI	Body mass index
BP	blood pressure
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed
FAS	full analysis set
GABA	gamma-aminobutyric acid
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISI	Insomnia Severity Index
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
LEM	lemborexant
LEM5	Lemborexant 5 mg
LEM10	Lemborexant 10 mg
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
OSA	obstructive sleep apnea
PBO	placebo
PGI-I	Patient Global Impression of Insomnia
PT	preferred term
QTcF	Difference between QTc corrected by Fridericia's formulas
SAE	Serious adverse events
SAS	safety analysis set
SDSB	Sleep Disorders Screening Battery
SE	sleep efficiency
SOC	system organ class
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
TIB	time in bed
TST	total sleep time

Abbreviation	Term
WASO	wake after sleep onset
ZOL	zolpidem
ZOL-ER	zolpidem tartrate extended release
ZOL-IR	zolpidem tartrate immediate release

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Title 21 of the United States Code of Federal Regulations [CFRs], Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate CRA[s], change of telephone number[s]). Documentation of IRB compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

Study progress is to be reported to IRBs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports, and inform the IRB of any reportable adverse events (AEs) per ICH guidelines and local IRB/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 within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB 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 (2013)
- ICH E6 Guideline for GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products,

Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the US CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

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

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

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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 15 investigational sites in the United States of America.

The name, telephone and fax numbers of the Medical Monitor and other contact personnel at the contract research organization(s) (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Indication

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

7.1.1 Current Therapeutic Options

Treatments for insomnia include both non-pharmacological (Schutte-Rodin, et al., 2008; Morgenthaler, et al., 2006) and pharmacological treatments (Sateia, et al., 2017). Patients who undergo thorough diagnostic evaluations for insomnia symptoms are asked about their sleep and wake habits, since some cases of insomnia can be addressed by improving sleep hygiene. Principles of good sleep hygiene include regular bedtimes and waketimes, limiting alerting activities before bedtime, and limiting caffeine and alcohol intake, among others (Schutte-Rodin, et al., 2008). These techniques are often not adequate to address insomnia symptoms (Stepanski and Wyatt, 2003; Irish, et al., 2015).

Another commonly recommended non-pharmacological approach is the use of cognitive behavioral therapy for insomnia (CBT-I; Schutte-Rodin, et al., 2008). CBT-I includes techniques to minimize wakefulness at the time the patient intends to sleep. However, while there are data to support the effectiveness of CBT-I, sleep restriction is commonly a major component, and this may lead to daytime sleepiness, an unintended consequence of short sleep (Kyle, et al., 2014). In contrast, lemborexant's mechanism of action would avoid the daytime sleepiness caused by sleep restriction, while reducing wakefulness and facilitating sleep, which is an important underlying goal of CBT-I.

There are numerous drugs available for the treatment of insomnia, some available by prescription and many available over-the-counter. Many of the over-the-counter medicines lack empirical data from adequate, well-designed and controlled clinical trials to support their use (Rosen, et al., 2005); these include melatonin and antihistamines. Pharmacological treatments available by prescription and used clinically for insomnia include sedative hypnotics (benzodiazepines, nonbenzodiazepine gamma-aminobutyric acid (GABA)-releasing [GABAergics] agents), sedating antidepressants, melatonin agonists, and a DORA.

7.1.2 Lemborexant

Lemborexant belongs to the pharmacologic class of orexin receptor antagonists, a class of chemical compounds developed for the treatment of insomnia. To date, clinical proof of concept has been achieved by 6 orexin receptor antagonists (lemborexant, almorexant [ACT-078573], suvorexant [MK-4305], filorexant [MK-6096]), seltorexant [MIN-202], and nemorexant [ACT-541468]), demonstrating validity of the mechanism of action (Herring, et al., 2012; Hoever, et al., 2012; Connor, et al., 2016; Murphy, et al., 2017; De Boer, et al., 2018).

Nonclinical data show that lemborexant binds to and competitively antagonizes human orexin-1 receptor (OX1R) and orexin-1 receptor (OX2R) in vitro, with rapid association and dissociation kinetics at both receptors. In vitro data show that lemborexant does not substantially interact with other sleep-related receptors and channels (Beuckmann, et al, 2017). Lemborexant prevents [Ala^{11}, D-Leu^{15}]-orexin-B-induced plasma adrenocorticotropic hormone increase in rats, and promotes physiological sleep in mice and rats. In mice, lemborexant does not promote sleep when the orexin pathway has been functionally impaired. In rats, daily treatment for 3 consecutive weeks with lemborexant did not result in tolerance or wakefulness rebound upon treatment cessation, and did not elicit direct transitions from wakefulness to rapid eye movement (REM) sleep, a narcolepsy-like symptom. However, in strong emotional contexts, lemborexant induced cataplexy-like events in mice (Study W-20140712). Cataplexy has been noted in dogs dosed with another orexin antagonist, suvorexant, when presented with food enrichment (Belsomra, 2018), but the relationship to cataplexy symptoms in humans has not been established. At doses up to 300 mg/kg (300-fold higher than necessary for sleep promotion), lemborexant did not have any negative influence on motor coordination in mice, nor did it show any significant interaction with ethanol.

7.1.2.1 Clinical Experience With Lemborexant

The safety and efficacy of lemborexant for the treatment of insomnia disorder was confirmed in 2 pivotal Phase 3 studies, E2006-G000-303 (Study 303) and E2006-G000-304 (Study 304). In Study 304, lemborexant also demonstrated superior improvement on objective and subjective measures of sleep onset and maintenance compared to zolpidem tartrate extended release (ZOL-ER). Additional safety assessments pertinent to insomnia drugs, specifically regarding postural stability, were also conducted in study E2006-A001-108 and Study 304. In these studies, the safety of lemborexant on postural stability was superior compared to zolpidem (ZOL). Based on these data, a New Drug Application for lemborexant was submitted to the US Food and Drug Administration for the treatment of insomnia disorder in December 2018 and accepted for review in February 2019.

The safety and tolerability of lemborexant has been comprehensively evaluated in a broad patient population that includes subjects with insomnia disorder per Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) (with or without medical or psychiatric comorbidities), subjects with Alzheimer's disease and ISWRD, subjects with mild obstructive sleep apnea (OSA), and subjects with severe renal impairment or mild to

moderate hepatic impairment. Exposures included dosing of ≥12 months. Approximately 40% of subjects in the development program were elderly (≥65 years), providing extensive safety and tolerability profile for this important subpopulation at risk for insomnia.

Overall, of 2835 subjects with sleep disorders, 1847 received lemborexant, 714 received placebo (PBO), and 263 received ZOL (extended release) and 11 received ZOL (immediate release). (revised per Amendment 02)

No deaths were reported in subjects treated with lemborexant.

The overall incidence of treatment-emergent serious adverse events (SAEs) for subjects treated with lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10) in the Phase 3 Pool was low (2.8% and 2.3%, respectively) but greater than for PBO (0.9%). However, when adjusted by duration of exposure, the overall incidence (subjects per patient-year) was similar to PBO (<0.1 for PBO, 0.1 for LEM5, and 0.1 for LEM10). The overall rate (events per patient-year) of treatment-emergent SAEs when adjusted by duration of exposure was <0.1 for PBO, <0.1 for LEM5, and <0.1 for LEM10.

There were no differences in the types of treatment-emergent SAEs reported during long-term treatment with lemborexant. There were no differences in treatment-emergent SAEs based on intrinsic factors, including age, sex, and body mass index (BMI) of subjects. Notably, the incidence of treatment-emergent SAEs in the elderly was consistent with that in younger subjects.

Across the Phase 3 studies of 303 and 304 (total subjects=1945), the majority of treatment-emergent SAEs occurred as singular events in 1 subject only. The SAEs of osteoarthritis (0% for PBO, 0.1% for LEM5, 0.4% for LEM10), rib fracture (0.2% for PBO, 0% for LEM5, 0.1% for LEM10), and diabetic neuropathy (0% for PBO, 0.3% for LEM5, 0% for LEM10) occurred in more than 1 subject across the PBO, LEM5, and LEM10 groups. One (0.1%) serious event of fall was reported in the LEM5 group.

7.1.2.2 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

None.

7.2 Study Rationale

Switching of medications for insomnia occurs often in clinical practice based on clinical response, AEs, reimbursement patterns, or physician and patient preference. However, there is no clinical trial experience or dosing guidance for transitioning from currently approved treatments for insomnia to lemborexant. Study E2006-A001-312 (Study 312) is designed as a pilot study to assess the dosing approach of directly transitioning from ZOL, the most commonly prescribed sleep aid (Bertisch, et al., 2014), to lemborexant, without tapering the ZOL dose, and with the opportunity for lemborexant dose titration. This study will provide initial information on patient satisfaction after switching to lemborexant, with secondary

objectives assessing subjective quality of sleep and tolerability. If issues are identified regarding patient satisfaction, tolerability, or quality of sleep, other dosing paradigms can be assessed in future studies to mitigate these issues.

7.2.1 Entry Criteria Rationale

Subjects with insomnia disorder per DSM-5 criteria (with or without medical or psychiatric comorbidities) will be eligible for study entry, which is representative of the typical target outpatient population. All subjects who are willing to substitute ZOL with LEM, regardless of the reason(s), will be eligible, and the reason(s) will be captured during screening. While it is anticipated that most eligible subjects would substitute ZOL with LEM due to dissatisfaction with ZOL, other reasons, as determined by input from Key Opinion Leaders (KOLs) in Sleep Medicine, may include, but are not limited to, concerns regarding ZOL side effects, eg, parasomnias. Including subjects with these various reasons is representative of the real-world outpatient setting.

While the approved dosing instructions for women and patients ≥65 stipulate that the lower dose of ZOL is to be prescribed, many women and elderly patients may be taking the higher dose. Therefore, for generalizability of the results of the study to the patient population, any stable dosing regimen will be eligible, including those subjects taking higher than approved doses up to the maximum approved (10 mg IR or 12.5 mg ER).

7.2.2 Rationale for Titration Schedule and Duration

Since this study is designed to reflect common clinical practice, flexibility to titrate the dose up or down is built into the dosing regimen. In the outpatient setting, clinicians typically advise patients to allow themselves one week to adjust to a new medication; therefore, subjects assigned to LEM5 will be encouraged to remain on their dose of LEM for 1-week prior to titrating up to LEM10, and those assigned to LEM10 will be encouraged to remain on their dose of LEM prior to titrating down to LEM5 after one week.

Subjects who intermittently use ZOL are expected to be more likely to be started on LEM5 in the outpatient setting, as they are not chronically exposed to, or reliant upon, pharmacologic insomnia treatments. Therefore, all subjects in Cohort 1 will be started on LEM5 during the Titration Period of the Treatment Phase.

The duration of the Treatment Phase of the Core Study is set at 2 weeks, since that amount of time is deemed reasonable by expert opinion from consultation with KOLs in Sleep Medicine for subjects to decide if they wish to continue on lemborexant.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking ZOL immediate release (ZOL-IR) or extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

8.2 Secondary Objectives (revised per Amendment 01)

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking ZOL

8.3 Exploratory Objectives (revised per Amendment 01)

- To evaluate LEM5 or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To compare nights on which an evening dose of LEM5 or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Total Sleep Time (TST)
    - Sleep Efficiency (SE)
    - Wake After Sleep Onset (WASO)
    - Wake Bouts
- To compare the daytime after an evening dose of LEM5 or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Sleep Bouts

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER. Adult (≥18 years) subjects are eligible for participation if they have been diagnosed with insomnia disorder per the DSM-5th Ed (American Psychiatric Association, 2014), are currently receiving ZOL as

monotherapy for insomnia, and who agree to substitute zolpidem tartrate immediate release (ZOL-IR) or ZOL-ER with LEM, regardless of the reason.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted. The Pretreatment and Treatment Phases will comprise the Core Study. The Extension Phase is described in detail in Appendix 3.

During the Screening Period, eligible subjects will continuously wear an actigraph and prospectively record the number of days ZOL is taken during the 3-week screening period using a Data Collection System. Based on ZOL use, subjects will be assigned to 1 of 2 cohorts of ZOL use frequency: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period
- The subjects who meet both criteria for intermittent and frequent ZOL use for 1 week each of the last 2 weeks of the 3-week Screening Period will be assigned to Cohort 1 and referred to as Cohort 1-Mixed. (revised per Amendment 02)

All subjects in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). Within Cohort 2, subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Subjects who remain eligible for the study will enter the Baseline Period, and continuously wear an actigraph during the Titration Period. (revised per Amendment 01)

Approximately 110 subjects will be screened to provide approximately 60 subjects for randomization (approximately 20 subjects in Cohort 1 and approximately 40 subjects in Cohort 2 [approximately 20 subjects each in LEM5 and LEM10]). (revised per Amendment 02)

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

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

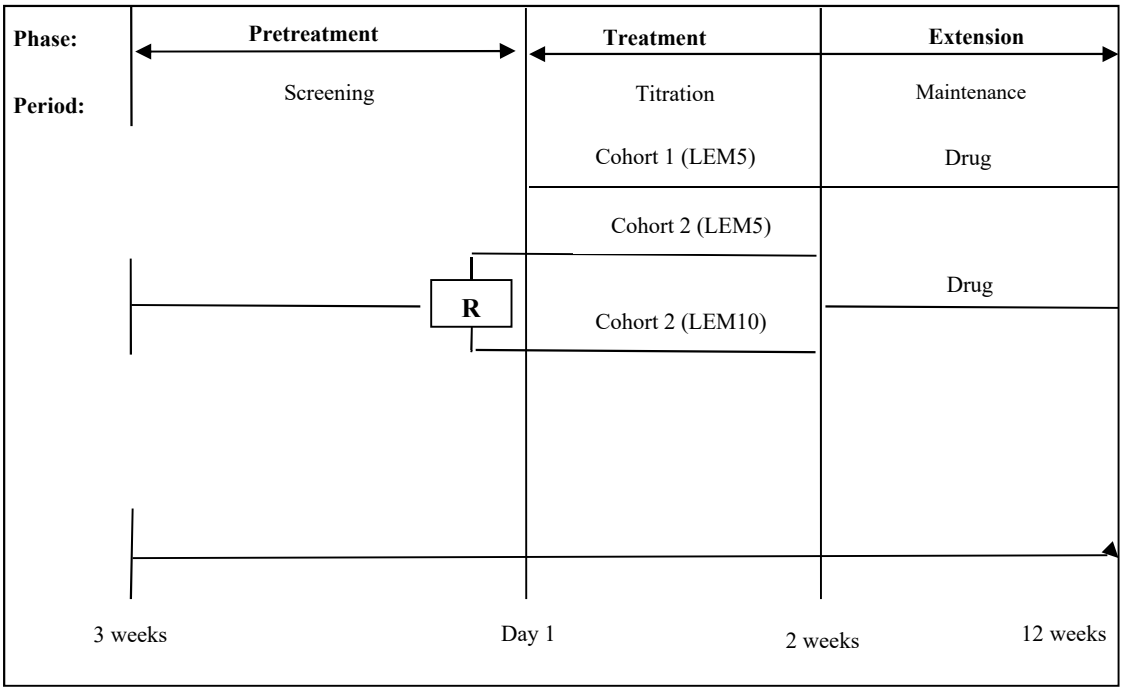

Figure 1 Study E2006-A001-312 – Study Design

LEM5 = lemborexant 5 mg, LEM5 = lemborexant 5 mg, R = Randomization

9.1.1 Pretreatment Phase (Core Study)

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

9.1.1.1 Screening Period (Core Study)

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. 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. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of insomnia per the DSM-5 (American Psychiatric Association, 2014), be currently receiving ZOL as monotherapy for insomnia, and agree to substitute zolpidem tartrate immediate release (ZOL-IR) or extended release (ZOL-ER) with LEM, regardless of the reason.

During the Screening Period, subjects will be required to bring the container of their currently prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record

the dose and frequency of ZOL which is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing this data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5 mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days of the 21-day Screening Period in order to be eligible for study inclusion. Eligible subjects will also be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period. Subjects will be provided with a daily log (sleep log) to note the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log. (revised per Amendment 01)

Subjects will return to clinic at the end of the Screening Period. Actigraph data will be downloaded and transmitted to the central reader, along with the sleep log of bedtimes, morning wake times, and the approximate times when the actigraph was replaced on the subject's wrist. (revised per Amendment 01)

For subjects who remain eligible for study enrollment, the second Screening Period visit will serve as that subject's Baseline Period, and will occur on the same day. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period
- The subjects who meet both criteria for intermittent and frequent ZOL use for 1 week each of the last 2 weeks of the 3-week Screening Period will be assigned to Cohort 1 and referred to as Cohort 1-Mixed. (revised per Amendment 02)

All subjects (approximately 20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (approximately 40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio. (revised per Amendment 02)

9.1.1.2 Baseline Period (Core Study)

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation, return their actigraphs and sleep logs to the study site, and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible by meeting the criteria for

inclusion/exclusion (Sections 9.3.1 and Section 9.3.2) will enter the Titration Period. (revised per Amendment 01)

9.1.2 Treatment Phase (Core Study)

The Treatment Phase will consist of a 2-week Titration Period and 1-day Follow-up Visit to occur 4 weeks after completion of the Titration Period (or as soon as possible following early discontinuation) for subjects not entering the Extension Phase. Subjects who meet all of the inclusion criteria and none of the exclusion criteria at the Baseline Visit, and who have entered ZOL medication use data into the Data Collection System for at least 14 of the 21-day Screening Period as specified in the Inclusion Criteria, are eligible to enter the Treatment Phase of the study.

9.1.2.1 Titration Period (Core Study)

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep. Subjects will continue to wear their actigraphs throughout the Titration Period, with the same instructions for use. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed with the subject at each visit during the Treatment and Extension Phases. Subjects will be instructed to not alter (ie break or cut) their tablets of LEM. (revised per Amendment 01)

Subjects assigned to Cohorts 1 and 2 will self-administer the study medication according to the following regimens:

- Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will decide when to take LEM according to their usual pattern, with the requirement that they take LEM at least once per week during the 2-week Titration Period. (revised per Amendment 01)
- Cohort 2 (Frequent ZOL Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For subjects starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For subjects starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the case report form (CRF).

Every morning, subjects will enter their insomnia drug use data into the data collection system and record their sleep log data, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each clinic visit except Follow-up Visit. (revised per Amendment 01)

Upon completion of the Titration Period, actigraphs will be returned to the study site, and subjects will be considered for eligibility to enter the Extension Phase (Appendix 3). (revised per Amendment 01)

9.1.2.2 Follow-Up Period

For subjects not entering the Extension Phase, the Follow-up Period will start immediately after the end of the Treatment Phase and last for 4 weeks. The purpose of the Follow-up Period is to assess adverse events and other safety parameters. Subjects will be instructed to continue insomnia management with the health-care provider who had been treating them prior to study entry, if they so desire.

9.1.3 Extension Phase

Subjects who complete the Core Study and wish to continue taking LEM will enter the 12-week Extension Phase. Subjects will continue the LEM dose and regimen established during the Titration Period; however, the dose may be titrated up or down depending on response and tolerability, per subject input and investigator judgement. For subjects who are eligible for the Extension Phase but who do not wish to continue study participation, the reason for discontinuation from the study will be recorded. At the end of the Extension Phase, the Follow-up Period will begin, and last for 4 weeks.

Details of the Extension Phase are provided in Appendix 3.

9.2 Discussion of Study Design, Including Choice of Control Groups

See Section 7.2, Study Rationale.

9.3 Selection of Study Population

Approximately 60 subjects will be enrolled at approximately 15 sites in the United States of America. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Male or female, 18 years or older, at the time of informed consent

2. Meets the DSM-5 criteria for Insomnia Disorder, either currently or prior to zolpidem use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month (revised per Amendment 01)
5. Confirmation of frequent or intermittent use of ZOL (based on review of drug use data). (revised per Amendment 02)

- Frequent use is defined as taking ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period (revised per Amendment 02)
- Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period; or taking ZOL as per the intermittent criteria for 1 week of the last 2 weeks of the 3-week Screening Period, and taking ZOL as per the frequent criteria for 1 week of the last 2 weeks of the 3-week Screening Period (revised per Amendment 02)

6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

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

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive serum pregnancy test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
2. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system (IUS)
     - a contraceptive implant

  - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation)
  - have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

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

3. Any history of moderate or severe OSA
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Drug use data do not confirm intermittent or frequent use as defined in the Inclusion Criterion No. 5 (revised per Amendment 02)
13. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
14. 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 (A list of prohibited concomitant medications is presented in the protocol).
15. Used any pharmacologic modality of treatment for insomnia other than ZOL, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period

16. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
17. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
18. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
19. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
20. Hypersensitivity to lemborexant or any of the excipients.
21. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
22. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
23. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
24. History of drug or alcohol dependency or abuse within approximately the last 2 years
25. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent.
26. 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.

9.4 Treatments

9.4.1 Treatment(s) Administered

The following treatments will be administered to subjects in the Core Study (Table 1).

Table 1 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
Lemborexant	5 mg	Tablet	1×5 mg tablets, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days
Lemborexant	10 mg	Tablet	1×10 mg tablet, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For Cohorts 1 and 2A (starting dose of LEM5), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For Cohort 2B (starting dose of LEM10), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the CRF.

9.4.2 Identity of Investigational Product

Lemborexant will be supplied by the sponsor in labeled containers.

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container. The sponsor will provide the study drug packaged as open-label supplies. Each subject's study drug will consist of lemborexant tablets supplied in bottles.

9.4.2.1 Chemical Name, Structural Formula of Lemborexant

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

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Based on ZOL use during the Screening Period, subjects will be assigned to 1 of 2 cohorts as shown below: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): taking ZOL at least 3 but fewer than 5 nights per week, for the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): taking ZOL at least 5 nights per week for the last 2 weeks of the 3-week Screening Period
- The subjects who meet both criteria for intermittent and frequent ZOL use for 1 week each of the last 2 weeks of the 3-week Screening Period will be assigned to Cohort 1 and referred to as Cohort 1-Mixed. (revised per Amendment 02)

All subjects (approximately 20) in Cohort 1 will receive LEM5. Subjects in Cohort 2 will be randomized to 1 of 2 Treatment Groups: Cohort 2A (approximately 20 subjects) will start on LEM5, and Cohort 2B (approximately 20 subjects) will start on LEM10. (revised per Amendment 02)

9.4.4 Selection of Doses in the Study

The doses to be administered are LEM5 and LEM10. In December 2018, these doses were submitted for approval in the US for the indication of insomnia. These doses were originally selected after conducting a dose-finding study (E2006-G000-201) after which their safety and efficacy were confirmed in 2 Phase 3 studies, Studies 303 and 304.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be provided a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time they intend to sleep. Subjects will be instructed on study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals. Subjects will be instructed not to alter (ie, break or cut) their tablets of LEM.

9.4.6 Blinding

This is an open-label study with randomization to treatment for subjects assigned to Cohort 2.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent or 30 days before first dose/administration of study drug, if appropriate) will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study.

9.4.7.1 Drug-Drug Interactions

Coadministration with moderate and strong CYP3A inhibitors may moderately increase exposure to lemborexant, and CYP3A inducers may markedly decrease lemborexant exposure. Drug interactions with lemborexant are described in further detail in the Investigator's Brochure; prohibited concomitant medications are described in Section 9.4.7.2 and listed in Appendix 2.

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.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (Appendix 2) should not be used during the study. A subject must discontinue any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

Prohibited medications include strong and moderate CYP3A inhibitors and all CYP3A inducers. Prohibited therapies also include: any pharmacologic treatment for insomnia disorder (with the exception of ZOL use during the Screening Period only); medications that are used for the purpose of inducing sleep (hypnotics) and medications that have known sedating effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications (Appendix 2) 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 2, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. Note that strong and moderate CYP3A inhibitors and all CYP3A4 inducers will not be permitted at any time for any duration during the study.

If a subject starts any prohibited medication or a new treatment/modality for insomnia disorder, he/she must discontinue from the study.

Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study. If subjects cannot comply after counseling, they may be discharged from the study.

9.4.8 Treatment Compliance

Compliance will be assessed by examination of bottles returned to the investigator at the end of the Titration Period.

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

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor. 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 [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type

prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance.

Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity.

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical, sleep, and psychiatric history will be recorded as designated in the Schedule of Procedures/Assessments (Table 3). All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations will be performed, as designated in the Schedule of Procedures/Assessments (Table 3). A full physical examination will include evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes) (revised per Amendment 02). The urogenital examination will be excluded (revised per Amendment 02), unless there are special circumstances and at the discretion of the investigator. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.2.2 Sleep Drug History Questionnaire

At Screening, subjects will complete a questionnaire reporting their history and response to prior sleep medications, as well as their motivation for participating in the study.

9.5.1.2.3 SLEEP DISORDER SCREENING BATTERY

A lifetime history of sleep disorders will be obtained only at the 1st Screening Visit. For insomnia complaints, this history will include clinical, qualitative assessment and/or confirmation that subjects meet diagnostic criteria for insomnia disorder. The history will also include information regarding habitual sleep timing, bedtime routines, and other aspects of sleep hygiene to determine eligibility and to exclude subjects whose insomnia symptoms appear to be due to poor sleep hygiene or to frequent napping, for example.

For the detection of other sleep disorders, the Sleep Disorders Screening Battery (SDSB) will be administered (see below).

The SDSB will include the following, to be self-administered by subjects:

- The STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA (Chung et al., 2008)
- The IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome (Abetz et al., 2006).

9.5.1.2.4 SLEEP DRUG EXPERIENCE INTERVIEW – ZOLPIDEM

At the end of the Screening Period, subjects will be asked questions about their subjective experiences while taking ZOL. The responses will be compared to the Sleep Drug Experience Interview – Lemborexant, which is done at the end of the Treatment Phase, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 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. The ISI will be completed at each study visit except Follow-up Visit.

9.5.1.3.2 PATIENT'S GLOBAL IMPRESSION – INSOMNIA

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep (Herring, et al., 2018). The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.3 Quality of Sleep Rating

The Quality of Sleep Rating (Krystal and Edinger, 2008) is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.4 Sleep Drug Experience Interview – Lemborexant

At the end of the Titration Period, subjects will be asked questions about their subjective experiences while taking LEM. The responses will be compared to the Sleep Drug Experience Interview – ZOL, which is done at the end of the Screening Period, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3.5 Actigraphy (revised per Amendment 01)

An actigraph is a device that consists of a compact, wrist-worn, battery-operated activity monitor that looks like a wrist watch. This device incorporates a multidirectional accelerometer to monitor degree and intensity of motion. Data from an actigraph are collected at a sampling rate of every 30 seconds and are scored as sleep or wake with a validated algorithm. Sleep/wake parameters are calculated from the scored data.

Eligible subjects will be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period, and, for those who qualify at the end of the Screening Period for study enrollment, during the Treatment Phase. Subjects will be provided with a daily log (sleep log) for noting the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log.

A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the subject.

Actigraphy data will be used to evaluate the following sleep and wake parameters for subjects during the Screening and Titration Periods:

- TST: The total time spent in sleep according to the epoch-by-epoch wake/sleep categorization during time in bed (TIB)
- SE: 100% × the total duration of sleep epochs during the defined nocturnal sleep period/TIB
- WASO: The total time spent awake according to the epoch-by-epoch wake/sleep categorization between sleep start (based on 'lights out') and 'got up'
- Wake Bouts: Wake of ≥ 5 minutes that occur during TIB
- Sleep Bouts: Continuous sleep ≥ 10 minutes that occur during Time Out of Bed (TOB)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity), regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations. Subjects will be asked about falls at every visit.

Sponsor's grading for laboratory values are presented in Appendix 1.

Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms (PTs) 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 [standard MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [faintness], and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events that meet serious criteria.

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal

relationship with the medicinal product. For this study, the study drug is lemborexant (in doses of 5 mg and 10 mg).

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, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase and for 7 days or 5× the half-life after the last dose, whichever is longer. SAEs will be collected for 28 days after the last dose or for 5× the half-life, whichever is longer.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

The number (percentage) of subjects with treatment emergent adverse events (TEAEs) of cataplexy or other events that are characterized according to the customized MedDRA query

PT as cataplexy related events will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately.

Customized MedDRA Queries for AEs that could potentially be considered cataplexy will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. All AEs must be followed for 28 days, or 5× the half-life, whichever is longer after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

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

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

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

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

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

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

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

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

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.

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

Not applicable. (revised per Amendment 02)

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

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	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Clinical laboratory tests during the Screening, Baseline, and Titration Periods will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

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

9.5.1.5.5 VITAL SIGNS, HEIGHT, AND WEIGHT MEASUREMENTS

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

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Documentation of the physical examination 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 Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

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

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

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

Columbia-Suicide Severity Rating Scale

The C-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Suicidality will be assessed as designated in the Schedule of Procedures and Assessments (Table 3), using a site-administered version of the C-SSRS (Posner, et al., 2011).

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 consecutive months as designated in the Schedule of Procedures/Assessments (Table 3).

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 3). This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, phencyclidine (PCP), opiates, benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments – Core Study

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Core Study.

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	**Pretreatment**			**Treatment**			
Period	**Screening**		**Baseline**	**Titration**	**Follow-Up[a]**		
Visit	**1**	**2a[b]**	**2b[b]**	**3[c]**		**ET[d,e]**	**UNS[e,f]**
Week	**-3 (Days -21 to -1)**	**-**	**0**	**2**	**6**		
Procedures/Assessments							
Demography	X						
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Sleep Drug History Questionnaire	X						
Sleep Disorder Screening Battery[g]	X						
Insomnia Severity Index	X	X[h]	X	X		X	X
C-SSRS	X	X[h]	X	X	X	X	X
Medical, sleep, psychiatric history	X						
Prior and concomitant medications	X	X[h]	X	X	X	X	X
Dispense study drug			X	X			
Retrieve unused study drug				X		X	
Study drug compliance				X		X	X
Physical examination[i]	X	X[h]	X	X	X	X	X
Vital signs and weight	X	X[h]	X	X	X	X	X

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	**Pretreatment**			**Treatment**			
Period	**Screening**		**Baseline**	**Titration**	**Follow-Up[a]**		
Visit	**1**	**2a[b]**	**2b[b]**	**3[c]**		**ET[d,e]**	**UNS[e,f]**
Week	**-3 (Days -21 to -1)**	**-**	**0**	**2**	**6**		
Procedures/Assessments							
Height	X						
Clinical laboratory tests[j]	X		X	X		X	X
Urine drug screen[k]	X	X[h]	X	X		X	X
Urine pregnancy test[l]	X	X[h]	X	X		X	X
Serum pregnancy test[l,m]	X						X
12-lead ECG[n]	X	X[h]	X	X		X	X
PGI-I[o]	X	X[h]	X	X		X	X
Quality of Sleep Rating[o]	X	X[h]	X	X		X	X
Sleep Drug Experience Interview - zolpidem		X				X	X
Sleep Drug Experience Interview - lemborexant				X			
Dispense actigraph	X						
Retrieve actigraph		X[p]		X		X	
Review data from data collection		X[h]	X	X		X	X

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	**Pretreatment**			**Treatment**			
Period	**Screening**		**Baseline**	**Titration**	**Follow-Up[a]**		
Visit	**1**	**2a[b]**	**2b[b]**	**3[c]**		**ET[d,e]**	**UNS[e,f]**
Week	**-3 (Days -21 to -1)**	**-**	**0**	**2**	**6**		
Procedures/Assessments							
system and sleep log							
Adverse events[q,r]	X	X[h]	X	X	X	X	X

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram, PGI-I = Patient Global Impression – Insomnia, T = Termination Visit, UNS = Unscheduled Visits
All visits to be done within ±7 days of the schedule, except for Visits 2, 3 and 4, which must be done within ±3 days.

a: The Follow-up Visit will be conducted 4 weeks after the End of Study Visit for subjects who completed the Titration Period but do not enter the Extension Phase.
b: Subjects will return to clinic at the end of the Screening Period. The Baseline Period will occur on the same day for subjects who remain eligible for study enrollment. Assessments conducted at the end of the Screening Period (Visit 2a) will serve as the assessments for the Baseline Period (Visit 2b) if a subject is enrolled into the Treatment Phase. Assessments will be performed once across Visit 2a and Visit 2b. Assessments to be conducted at Baseline (but which are not done at Visit 2a) will include clinical laboratory tests and dispensing of study drug.
c: This visit will represent the End of Study Visit for subjects who completed the Titration Period but are not entering the Extension Phase. Subjects should otherwise enter the Extension Phase immediately after completion of the Titration Period of the Core Study, in which case this visit will also serve as the first visit of the Extension Phase.
d: Subjects who discontinue study drug prematurely at any time after entering the Treatment Phase will be encouraged to return to the site as soon as practicable (preferably within 7 days) to complete the Early Termination Visit.
e: ECG will only be done during Early Termination and Unscheduled Visits if the results from the previous visit were deemed to be clinically significant by the investigator.
f: Assessments during Unscheduled Visits will be conducted at the discretion of the investigator.
g: Sleep Disorders Screening Battery comprises: STOP Bang and International Restless Legs Scale.
h: Data for Visit 2a will represent the Baseline Period (Visit 2b) assessment if the subject is enrolled. Assessments will be performed once across Visit 2a and Visit 2b.
i: A full physical examination will be conducted at Visit 1. A brief physical examination will be conducted (including head, eyes, ears, nose, throat, heart, lungs, abdomen, and extremities, and at the discretion of the investigator, other physical conditions of note) at Visit 2a, Visit 3, and at the Follow-up Visit. For Early Termination and Unscheduled Visits, a physical examination will be conducted at the discretion of the investigator. (revised per Amendment 02)
j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
k: Urine drug test at Unscheduled Visits will be conducted at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an AE
l: Female subjects of child-bearing potential only.
m: To be conducted at Visit 1, and if urine pregnancy testing is positive.
n: The ECG should be repeated if a clinically significant (as determined by the investigator) abnormality is observed.
o: From the beginning of the Pretreatment Phase to the end of the Treatment Phase, and provided an insomnia drug was taken the night prior, PGI-I and Sleep Quality Rating data will be entered into the electronic data capture system by the subject.
p: Actigraphs will be collected from subjects who do not meet Screening criteria after data review at Visit 2a. (revised per Amendment 01)
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 9.5.1.5, Adjudication Committee.
r: 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 its resolution. (revised per Amendment 01)

Table 5 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

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

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of nighttime sleep and daytime impairment complaints, the ISI will be evaluated for changes from baseline.

The PGI-I has been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. The C-SSRS, a standardized assessment required by regulatory authorities, will be used to evaluate any effects of lemborexant on suicidality.

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 in the Treatment Phase, 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 of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

A congenital anomaly, death during perinatal period, 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

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Not applicable

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

Not applicable.

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 (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

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

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic response, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event CRF.

Sites will be assessed for the appropriateness of study drug storage and retrieval at the time of site selection. Required policies and procedures will be clearly communicated to the site to assess the site's capabilities and adherence to storage, dispensing, reconciliation, and retention of study drug.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and a snapshot of the database is obtained and released) and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. The study endpoints for efficacy and safety will presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

This study is designed to reflect clinical practice, in which patient satisfaction of the treatment after switching is an important consideration for maintaining a patient on that treatment. This was the basis for defining the outcome of transition to lemborexant. While sleep quality assessments are included as secondary outcomes in this pilot study to supplement the Phase 3 clinical trial data, it is not necessary to establish the absolute amount of improvement in sleep parameters, but rather whether the subject is satisfied enough to continue treatment with lemborexant.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses or preference to continue insomnia management with another health care provider).

9.7.1.1.2 SECONDARY ENDPOINTS (REVISED PER AMENDMENT 01)

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

9.7.1.1.3 EXPLORATORY ENDPOINTS (REVISED PER AMENDMENT 01)

The exploratory endpoints are as follows:

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment

- To compare nights on which an evening dose of LEM5 or LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- To compare the daytime after an evening dose of LEM5 or LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Mean Duration of Sleep Bouts

9.7.1.2 Definitions of Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the FAS.

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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by randomized treatment groups.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each randomized and end of the Titration Period treatment groups using descriptive statistics. Continuous demographic variables include age, height, weight, and BMI; categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (<18.5, 18.5 to <25, 25 to ≥30), race, and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using ISI, PGI-I, and Quality of Sleep Rating.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization WHO Drug Global March 2019 or later. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by randomized treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD PT.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be conducted on the FAS. Efficacy endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan. (revised per Amendment 01)

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES (REVISED PER AMENDMENT 01)

The secondary analyses are as follows:

- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was “just right” at the end of the Titration Period (as data allow) will be reported.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES (REVISED PER AMENDMENT 01)

- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups.

- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of Titration Period dose groups.
- Average value of following sleep-related actigraphy variables will be summarized by treatment over the nights on which an evening dose of LEM5, LEM10, and ZOL was taken.
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- Average value of wake-related actigraphy variable, mean duration of Sleep Bouts will be summarized by treatment over the daytime after an evening dose of LEM5, LEM10, and ZOL was taken.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.

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.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of AEs will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

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

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

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to a Customized MedDRA Query (CMQ) PT as cataplexy-related events, as well drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately. In addition, 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, as per the Adjudication Committee description.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and end of Titration Period dose using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

9.7.1.8.4 VITAL SIGNS

Mean changes from baseline in vital signs (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and out-of-range vital signs will be summarized by end of Titration Period dose groups for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

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 4). 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 (Safety Analysis Set), by end of Titration Period dose and time point.

Table 4 Clinically Notable Vital Sign Criteria

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

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at Screening and at the end of the Titration Period. The incidence of abnormal ECG findings will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL Use) and Cohort 2 (Frequent ZOL Use) using descriptive statistics. Shift tables will present changes from baseline in ECG interpretation (categorized as normal and abnormal) by time point.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

Urine drug test results and pregnancy test results will also be listed.

9.7.2 Determination of Sample Size

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll approximately 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for ZOL. Approximately 20 subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This

sample size is deemed sufficient to inform whether the proposed strategies are sufficient to determine whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM. (revised per Amendment 02)

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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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 should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as Interactive Voice/Web Response System (IxRS), x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

- Electronic Patient-Reported Outcome by self-reported measures

11.4 Recording of Data

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

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

The efficacy assessments are evaluated based on the data entered into electronic Patient-Reported Outcome. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

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

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, 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 principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designated contractor, or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/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.

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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				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, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	• Barbiturates • Benzodiazepines • gamma-aminobutyric acid (GABA) analogues • Hydantoins • Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter [OTC])	• Diphenhydramine HCl • Carbinoxamine • Doxylamine • Dimenhyrinate • Triprolidine • Bromopheniramine • Chlorphenamine • Hydroxazine
Antihistamines with known sedating effects	• Non-sedating, eg, Claritin™ is not prohibited
Anxiolytics with known sedating effects	• Lorazepam • Alprazolam • Buspirone

Category	Medication
Strong CYP3A inhibitors	• Amiodarone • Bocepravir • Clarithomycin • Cobicistat • Conivaptan • Danoprevir • Diltizem • Elteravir • Fluvoxamine • Grapefruit juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telapravir • Telethromycin • Tipranavir • Troleandomycin • Voriconazole
Moderate CYP3A inhibitors	• Amprenavir • Aprepitant • Atazanavir • Casopitant • Cimetidine • Ciprofloxacin • Clotrimazole • Crizotinib • Cyclosporin • Darunavir • Dronadarone • Erythromycin • Faldaprevir • Fluconazole • Fluvoxamine • Imatinib • Netupitant • Tofisopam • Verapamil

Category	Medication
Cytochrome P450 (CYP)3A inducers	• Avasimibe • Bosentan • Carbamazepine • Efavirenz • Enzaluteamide • Etravirine • Lersivirine • Modafinil • Mitotane • Nafcillin • Phenobarbital • Phenytoin • Rifabutin • Rifampin • St John's Wort • Troglitazone • Talviraline • Thioridazine
Hypnotics	• Melatonin • Prescribed or OTC
Herbal preparations with sedating effects	• -
Monoamine oxidase inhibitors (MAOIs)	• -
Opioid Analgesics	• -
Muscle relaxants (centrally-acting) with known sedating effects	• GABA analogues • Hydantoins • Phenyltriazines
Other	• Warfarin, heparin, ticlopidine • Systemic isoretinoin • Systemic glucocorticoids

Appendix 3 Extension Phase

Study Design and Plan

The Extension Phase comprises a Maintenance Period of up to 12 weeks in duration, and a Follow-up Period visit that is to occur 4 weeks after the end of the Maintenance Period.

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of Lemborexant (LEM) that they took at the end of the Titration Period. Subjects will subsequently return to clinic at the visit as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, and study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Maintenance Period).

End of Study

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

Study Drug Supplies

Subjects will enter the Extension Phase from the Titration Phase of the Core Study, taking the same dose of LEM that was their final dose of the Titration Phase, ie, LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Schedule of Procedures/Assessments

Table 5 presents the Schedule of Procedures and Assessments for the 12-week Extension Phase.

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 – Extension (revised per Amendment 01)

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				
C-SSRS	X	X	X	X
Prior and concomitant medications	X	X	X	X
Study drug compliance	X		X	X
Dispense study drug				
Retrieve unused study drug	X		X	X
Physical examination[e]	X	X	X	X
Vital signs and weight	X	X	X	X
Clinical laboratory tests[f]	X		X	X
Urine drug screen[g]	X		X	X
Urine pregnancy test[h]	X		X	X
Serum pregnancy test[h,i]				X
12-Lead ECG[j]	X		X	X
Adverse events[k,l]	X	X	X	X

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 – Extension (revised per Amendment 01)

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram.

All visits to be done within ±7 days of the schedule.

a: The Follow-up Visit will be conducted 4 weeks after the end of the Extension Phase.
b: Subjects who discontinue study drug prematurely at any time after entering the Extension will be encouraged to return to the site as soon as practicable (preferably within 7 days).
c: During Early Termination and unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.
d: Assessments during an Unscheduled Visit to be conducted at the discretion of the investigator.
e: A full physical examination will be conducted at Visit 4 and 5. For Early Termination and Unscheduled Visits, a full physical examination will be conducted at the discretion of the investigator. (revised per Amendment 02)
f: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
g: Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
h: Female subjects of child-bearing potential only.
i: To be conducted if urine pregnancy testing is positive
j: The ECG should be repeated if a clinically significant abnormality (as determined by the investigator) is observed.
k: 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 9.5.1.5, Adjudication Committee
l: If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or severe unexpected AE and at its resolution. (revised per Amendment 01)

Statistical Analyses

All statistical analyses will be the responsibility of the Biostatistics Department of Eisai. Statistical programming and analyses will be performed using SAS or other validated software.

Safety Analyses

The primary focus of data summarization for the Extension Phase will be on safety and tolerability. Evaluations of safety data will be performed on the Safety Analysis Set.

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-312

Study Protocol Title: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia

Investigational Product Name: E2006\Lemborexant

IND Number: 111871

SIGNATURES

Authors:

PPD

Eisai, Inc

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Investigational Product Name:	E2006\Lemborexant
IND Number:	111871

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International 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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 2.0

New version /date: Version 3.0/03 Jun 2019 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Addition of actigraphy	To provide objective data on the effect of LEM and ZOL on sleep and wake parameters	Section 2 – Exploratory Objectives Section 2 – Study Design Section 2 – Efficacy Assessments (Core Study only) Section 2 – Statistical Methods Section 2 – Efficacy Analyses (Core Study only) Section 8.3 Section 9.1.1.1 Section 9.1.1.2 Section 9.1.2.1 Section 9.5.1.3.5 Section 9.7.1.1.3 Section 9.7.1.6.3 Table 3
Reorganization of secondary and exploratory objectives and endpoints	To focus secondary endpoints on successful transition due to dose-related aspects of LEM	Section 2 – Secondary Objectives Section 2 – Exploratory Objectives Section 8.2 Section 8.3 Section 9.7.1.1.2 Section 9.7.1.1.3 Section 9.7.1.6.2 Section 9.7.1.6.3
Clarification of cohort assignment based on ZOL use frequency	Clarification	Section 2 – Study Design Section 2 - Inclusion Criteria Section 2 - Exclusion Criteria Section 9.1 Section 9.1.1.1 Section 9.1.2.1 Section 9.3.1 Section 9.3.2 Section 9.4.3
Clarification of PK sampling in the event of an SAE or severe unexpected AE and its resolution	Clarification	Table 3 Table 5
Clarification of data collection at Visit 2a	Clarification	Table 3

Revisions to Version 1.0

New version /date: Version 2.0/12 Apr 2019

Change	Rationale	Affected Protocol Sections
Modified the text in Exclusion Criterion No. 1 to replace urine pregnancy test with serum pregnancy test.	Administrative change	• Synopsis –Exclusion criteria • Section 9.3.2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	E2006/Lemborexant
Indication:	Insomnia
Phase:	3b
	V1.0 12 Apr 2019 (original protocol)
	V2.0 12 Apr 2019 (revised original protocol)
	V3.0 03 Jun 2019 (Amendment 01)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for 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, Pilot Study to Evaluate Next-Dose Transition From Zolpidem to Lemborexant for the Treatment of Insomnia

Investigator(s)

Unknown

Sites

Approximately 15 sites within the United States of America

Study Period and Phase of Development

Phase 3b pilot study

Estimated duration of up to 38 weeks from first subject in to last subject's last visit.

Objectives

Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking zolpidem tartrate immediate release (ZOL-IR) or zolpidem tartrate extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

Secondary Objectives (revised per Amendment 01)

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking zolpidem (ZOL)

Exploratory Objectives (revised per Amendment 01)

- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To compare nights on which an evening dose of LEM, LEM5, and LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Total Sleep Time (TST)
    - Sleep Efficiency (SE)
    - Wake After Sleep Onset (WASO)
    - Wake Bouts
- To compare the daytime after an evening dose of LEM, LEM5, and LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Sleep Bouts

Study Design

E2006-A001-312 is a multicenter Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. The Pretreatment and Treatment Phases will comprise the Core Study. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted.

Core Study

Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

Screening Period

During the Screening Period, subjects will be required to bring the container of their prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the frequency of ZOL is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing these data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days out of the allowable 21-day Screening Period in order to be eligible for study inclusion. Eligible subjects will also be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period. Subjects will be provided with a daily log (sleep log) to note the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log. (revised per Amendment 01)

Subjects will return to clinic at the end of the Screening Period. Actigraph data will be downloaded and transmitted to the central reader, along with the sleep log of bedtimes, morning wake times, and the approximate times when the actigraph was replaced on the subject's wrist. (revised per Amendment 01)

Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks of the 3-week Screening Period, or (revised per Amendment 01)
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Baseline Period

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation, return their actigraphs and sleep logs to the study site, and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible will enter the Titration Period. (revised per Amendment 01)

Treatment Phase

Titration Period

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep at night. Subjects will continue to wear their actigraphs throughout the Titration Period, with the same instructions for use. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed. Subjects will be instructed to not alter (ie, break or cut) their tablets of LEM. (revised per Amendment 01)

Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will decide when to take LEM according to their usual pattern, with the requirement that they take LEM at least once per week during the 2-week Titration Period. (revised per Amendment 01)

Cohort 2 (Frequent Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

For subjects with a starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site should they feel that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.

For subjects with a starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site should they feel that LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of LEM dose change during the Core Study, the reason for the dose change will be recorded in the case report form (CRF). Subjects will be allowed 1 LEM dose adjustment during the Titration Period. Every morning, subjects will enter their insomnia drug use data into the data collection system and record their sleep log data, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each study visit except Follow-up Visit. (revised per Amendment 01)

Upon completion of the Titration Period, actigraphs will be returned to the study site, and subjects will be considered for eligibility to enter the Extension Phase. (revised per Amendment 01)

Extension Phase

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of LEM that they took at the end of the Titration Period. Subjects will subsequently return to clinic as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Treatment Phase for subjects not entering the Extension Phase or after the end of the Extension Phase, for subjects entering the Extension Phase).

End of Study

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

Number of Subjects

Approximately 110 subjects will be screened to provide approximately 60 subjects (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 in LEM5, 20 in LEM10]).

Inclusion Criteria

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) criteria for Insomnia Disorder, either currently or prior to ZOL use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

Exclusion Criteria

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

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

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

3. Any history of moderate or severe obstructive sleep apnea (OSA)
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Reports intermittent or frequent use of ZOL at Visit 1 which is not confirmed, based on review of drug use data, at Visit 2a. Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)
13. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
14. 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 (A list of prohibited concomitant medications is presented in the protocol).
15. Used any pharmacologic modality of treatment for insomnia other than zolpidem, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
16. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
17. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
18. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
19. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
20. Hypersensitivity to lemborexant or any of the excipients.
21. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.

22. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
23. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years
24. History of drug or alcohol dependency or abuse within approximately the last 2 years
25. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent
26. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Core Study

Test drug:

LEM5 or LEM10 taken orally in tablet form at night within a few minutes of the time the subject intends to sleep, according to the subject's predetermined intermittent or frequent use schedule.

Comparator Drug: Not applicable

Extension Phase

Test drug:

LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Duration of Treatment

A maximum of 14 weeks:

2 weeks of LEM5 and/or LEM10 during the Treatment Phase of the Core Study,

12 weeks during the Extension Phase

Concomitant Drug/Therapy

Prohibited medications should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Phase.
Prohibited medications include moderate and strong cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers, and medications that have known sedating effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).
If a medication is not on the list of prohibited medications but in the opinion of the investigator causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.
If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study. Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study.

Assessments

Screening Assessments (Core Study only)

Sleep Disorders Screening Battery (SDSB):

The SDSB will include:

- STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA
- IRLS: a subjective scale comprising 10 questions, which measures severity of symptoms of restless legs syndrome

Sleep Drug History Questionnaire

Subjects will be asked questions about their history and response to prior sleep medications.

Sleep Drug Experience Interview – Zolpidem

Subjects will be asked questions about their subjective experiences while taking ZOL at the end of the Screening Period.

Efficacy Assessments (Core Study only)

Patient Global Impression – Insomnia

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep. The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening.

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. The ISI will be completed at each study visit except Follow-up Visit.

Quality of Sleep Rating

The Quality of Sleep Rating is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

Sleep Drug Experience Interview – Lemborexant

Subjects will be asked questions about their subjective experiences while taking LEM at the end of the Titration Period.

Actigraphy (revised per Amendment 01)

An actigraph is a device that consists of a compact, wrist-worn, battery-operated activity monitor that looks like a wrist watch. This device incorporates a multidirectional accelerometer to monitor degree and intensity of motion. Data from an actigraph are collected at a sampling rate of every 30 seconds and are scored as sleep or wake with a validated algorithm. Sleep/wake parameters are calculated from the scored data. A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the subject. Actigraphy data will be used to evaluate the following sleep and wake parameters for subjects during the Screening and Titration Periods:

- TST: The total time spent in sleep according to the epoch-by-epoch wake/sleep categorization during time in bed (TIB)

- SE: 100% × the total duration of sleep epochs during the defined nocturnal sleep period/TIB
- WASO: The total time spent awake according to the epoch-by-epoch wake/sleep categorization between sleep start (based on 'lights out') and 'got up'
- Wake Bouts: Wake of ≥ 5 minutes that occur during TIB
- Sleep Bouts: Continuous sleep ≥ 10 minutes that occur during Time Out of Bed (TOB)

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments (Core Study and Extension Phase)

Safety assessments will consist of monitoring and recording all adverse events (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. Subjects will be asked about falls at every visit.

Adjudication Committee

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

Columbia – Suicide Severity Rating Scale

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

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments.

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments. This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, PCP, opiates, benzodiazepines, barbiturates, and amphetamines.

Bioanalytical Methods

Not applicable.

Statistical Methods

The study endpoints for efficacy and safety will be presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed.

Primary Endpoint

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses, or preference to continue insomnia management with another health care provider).

Secondary Endpoints (revised per Amendment 01)

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

Exploratory Endpoints (revised per Amendment 01)

The exploratory endpoints are as follows:

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.
- To compare nights on which an evening dose of LEM, LEM5, and LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- To compare the daytime after an evening dose of LEM, LEM5, and LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Mean Duration of Sleep Bouts

Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the Full Analysis Set.

Efficacy Analyses (Core Study only)

All efficacy analyses will be conducted on the FAS.

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.
- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall,
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of the Titration Period dose groups.
- Average value of following sleep-related actigraphy variables will be summarized by treatment over the nights on which an evening dose of LEM, LEM5, LEM10, and ZOL was taken. (revised per Amendment 01)
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- Average value of wake-related actigraphy variable, mean duration of Sleep Bouts will be summarized by treatment over the daytime after an evening dose of LEM, LEM5, LEM10, and ZOL was taken. (revised per Amendment 01)

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses (Core Study and Extension Phase)

Evaluations of safety data will be performed on the SAS.

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics using end of titration dose group. AEs

summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.
Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and PTs related to drug abuse liability, will be summarized seperately. The results of the deliberation of the Adjudication Committee will be reported separately. In addition, 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, as per the Adjudication Committee description.

Other Analyses (Core Study)

Efficacy endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan. (revised per Amendment 01)

Interim Analyses

No interim analyses are planned for this study.

Sample Size Rationale

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for zolpidem. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to evaluate whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BMI	Body mass index
BP	blood pressure
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed
FAS	full analysis set
GABA	gamma-aminobutyric acid
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISI	Insomnia Severity Index
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
LEM	lemborexant
LEM5	Lemborexant 5 mg
LEM10	Lemborexant 10 mg
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
OSA	obstructive sleep apnea
PBO	placebo
PGI-I	Patient Global Impression of Insomnia
PT	preferred term
QTcF	Difference between QTc corrected by Fridericia's formulas
SAE	Serious adverse events
SAS	safety analysis set
SDSB	Sleep Disorders Screening Battery
SE	sleep efficiency
SOC	system organ class
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
TIB	time in bed
TST	total sleep time

Abbreviation	Term
WASO	wake after sleep onset
ZOL	zolpidem
ZOL-ER	zolpidem tartrate extended release
ZOL-IR	zolpidem tartrate immediate release

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Title 21 of the United States Code of Federal Regulations [CFRs], Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate CRA[s], change of telephone number[s]). Documentation of IRB compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

Study progress is to be reported to IRBs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports, and inform the IRB of any reportable adverse events (AEs) per ICH guidelines and local IRB/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 within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB 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 (2013)
- ICH E6 Guideline for GCP (Committee for Proprietary Medicinal Products [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 US CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

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

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

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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 15 investigational sites in the United States of America.

The name, telephone and fax numbers of the Medical Monitor and other contact personnel at the contract research organization(s) (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Indication

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

7.1.1 Current Therapeutic Options

Treatments for insomnia include both non-pharmacological (Schutte-Rodin, et al., 2008; Morgenthaler, et al., 2006) and pharmacological treatments (Sateia, et al., 2017). Patients who undergo thorough diagnostic evaluations for insomnia symptoms are asked about their sleep and wake habits, since some cases of insomnia can be addressed by improving sleep hygiene. Principles of good sleep hygiene include regular bedtimes and waketimes, limiting alerting activities before bedtime, and limiting caffeine and alcohol intake, among others (Schutte-Rodin, et al., 2008). These techniques are often not adequate to address insomnia symptoms (Stepanski and Wyatt, 2003; Irish, et al., 2015).

Another commonly recommended non-pharmacological approach is the use of cognitive behavioral therapy for insomnia (CBT-I; Schutte-Rodin, et al., 2008). CBT-I includes techniques to minimize wakefulness at the time the patient intends to sleep. However, while there are data to support the effectiveness of CBT-I, sleep restriction is commonly a major component, and this may lead to daytime sleepiness, an unintended consequence of short sleep (Kyle, et al., 2014). In contrast, lemborexant's mechanism of action would avoid the daytime sleepiness caused by sleep restriction, while reducing wakefulness and facilitating sleep, which is an important underlying goal of CBT-I.

There are numerous drugs available for the treatment of insomnia, some available by prescription and many available over-the-counter. Many of the over-the-counter medicines lack empirical data from adequate, well-designed and controlled clinical trials to support their use (Rosen, et al., 2005); these include melatonin and antihistamines. Pharmacological treatments available by prescription and used clinically for insomnia include sedative hypnotics (benzodiazepines, nonbenzodiazepine gamma-aminobutyric acid (GABA)-releasing [GABAergics] agents), sedating antidepressants, melatonin agonists, and a DORA.

7.1.2 Lemborexant

Lemborexant belongs to the pharmacologic class of orexin receptor antagonists, a class of chemical compounds developed for the treatment for insomnia. To date, clinical proof of concept has been achieved by 6 orexin receptor antagonists (lemborexant, almorexant [ACT-078573], suvorexant [MK-4305], filorexant [MK-6096]), seltorexant [MIN-202], and nemorexant [ACT-541468]), demonstrating validity of the mechanism of action (Herring, et al., 2012; Hoever, et al., 2012; Connor, et al., 2016; Murphy, et al., 2017; De Boer, et al., 2018).

Nonclinical data show that lemborexant binds to and competitively antagonizes human orexin-1 receptor (OX1R) and orexin-1 receptor (OX2R) in vitro, with rapid association and dissociation kinetics at both receptors. In vitro data show that lemborexant does not substantially interact with other sleep-related receptors and channels (Beuckmann, et al, 2017). Lemborexant prevents [Ala^{11}, D-Leu^{15}]-orexin-B-induced plasma adrenocorticotropic hormone increase in rats, and promotes physiological sleep in mice and rats. In mice, lemborexant does not promote sleep when the orexin pathway has been functionally impaired. In rats, daily treatment for 3 consecutive weeks with lemborexant did not result in tolerance or wakefulness rebound upon treatment cessation, and did not elicit direct transitions from wakefulness to rapid eye movement (REM) sleep, a narcolepsy-like symptom. However, in strong emotional contexts, lemborexant induced cataplexy-like events in mice (Study W-20140712). Cataplexy has been noted in dogs dosed with another orexin antagonist, suvorexant, when presented with food enrichment (Belsomra, 2018), but the relationship to cataplexy symptoms in humans has not been established. At doses up to 300 mg/kg (300-fold higher than necessary for sleep promotion), lemborexant did not have any negative influence on motor coordination in mice, nor did it show any significant interaction with ethanol.

7.1.2.1 Clinical Experience With Lemborexant

The safety and efficacy of lemborexant for the treatment of insomnia disorder was confirmed in 2 pivotal Phase 3 studies, E2006-G000-303 (Study 303) and E2006-G000-304 (Study 304). In Study 304, lemborexant also demonstrated superior improvement on objective and subjective measures of sleep onset and maintenance compared to zolpidem tartrate extended release (ZOL-ER). Additional safety assessments pertinent to insomnia drugs, specifically regarding postural stability, were also conducted in study E2006-A001-108 and Study 304. In these studies, the safety of lemborexant on postural stability was superior compared to zolpidem (ZOL). Based on these data, a New Drug Application for lemborexant was submitted to the US Food and Drug Administration for the treatment of insomnia disorder in December 2018 and accepted for review in February 2019.

The safety and tolerability of lemborexant has been comprehensively evaluated in a broad patient population that includes subjects with insomnia disorder per Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) (with or without medical or psychiatric comorbidities), subjects with Alzheimer's disease and ISWRD, subjects with mild obstructive sleep apnea (OSA), and subjects with severe renal impairment or mild to

moderate hepatic impairment. Exposures included dosing of ≥12 months. Approximately 40% of subjects in the development program were elderly (≥65 years), providing extensive safety and tolerability profile for this important subpopulation at risk for insomnia.

Overall, of 2824 subjects with sleep disorders, 1848 received lemborexant, 714 received placebo (PBO), and 263 received ZOL.

No deaths were reported in subjects treated with lemborexant.

The overall incidence of treatment-emergent serious adverse events (SAEs) for subjects treated with lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10) in the Phase 3 Pool was low (2.8% and 2.3%, respectively) but greater than for PBO (0.9%). However, when adjusted by duration of exposure, the overall incidence (subjects per patient-year) was similar to PBO (<0.1 for PBO, 0.1 for LEM5, and 0.1 for LEM10). The overall rate (events per patient-year) of treatment-emergent SAEs when adjusted by duration of exposure was <0.1 for PBO, <0.1 for LEM5, and <0.1 for LEM10.

There were no differences in the types of treatment-emergent SAEs reported during long-term treatment with lemborexant. There were no differences in treatment-emergent SAEs based on intrinsic factors, including age, sex, and body mass index (BMI) of subjects. Notably, the incidence of treatment-emergent SAEs in the elderly was consistent with that in younger subjects.

Across the Phase 3 studies of 303 and 304 (total subjects=1945), the majority of treatment-emergent SAEs occurred as singular events in 1 subject only. The SAEs of osteoarthritis (0% for PBO, 0.1% for LEM5, 0.4% for LEM10), rib fracture (0.2% for PBO, 0% for LEM5, 0.1% for LEM10), and diabetic neuropathy (0% for PBO, 0.3% for LEM5, 0% for LEM10) occurred in more than 1 subject across the PBO, LEM5, and LEM10 groups. One (0.1%) serious event of fall was reported in the LEM5 group.

7.1.2.2 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

None.

7.2 Study Rationale

Switching of medications for insomnia occurs often in clinical practice based on clinical response, AEs, reimbursement patterns, or physician and patient preference. However, there is no clinical trial experience or dosing guidance for transitioning from currently approved treatments for insomnia to lemborexant. Study E2006-A001-312 (Study 312) is designed as a pilot study to assess the dosing approach of directly transitioning from ZOL, the most commonly prescribed sleep aid (Bertisch, et al., 2014), to lemborexant, without tapering the ZOL dose, and with the opportunity for lemborexant dose titration. This study will provide initial information on patient satisfaction after switching to lemborexant, with secondary objectives assessing subjective quality of sleep and tolerability. If issues are identified

regarding patient satisfaction, tolerability, or quality of sleep, other dosing paradigms can be assessed in future studies to mitigate these issues.

7.2.1 Entry Criteria Rationale

Subjects with insomnia disorder per DSM-5 criteria (with or without medical or psychiatric comorbidities) will be eligible for study entry, which is representative of the typical target outpatient population. All subjects who are willing to substitute ZOL with LEM, regardless of the reason(s), will be eligible, and the reason(s) will be captured during screening. While it is anticipated that most eligible subjects would substitute ZOL with LEM due to dissatisfaction with ZOL, other reasons, as determined by input from Key Opinion Leaders (KOLs) in Sleep Medicine, may include, but are not limited to, concerns regarding ZOL side effects, eg, parasomnias. Including subjects with these various reasons is representative of the real-world outpatient setting.

While the approved dosing instructions for women and patients ≥65 stipulate that the lower dose of ZOL is to be prescribed, many women and elderly patients may be taking the higher dose. Therefore, for generalizability of the results of the study to the patient population, any stable dosing regimen will be eligible, including those subjects taking higher than approved doses up to the maximum approved (10 mg IR or 12.5 mg ER).

7.2.2 Rationale for Titration Schedule and Duration

Since this study is designed to reflect common clinical practice, flexibility to titrate the dose up or down is built into the dosing regimen. In the outpatient setting, clinicians typically advise patients to allow themselves one week to adjust to a new medication; therefore, subjects assigned to LEM5 will be encouraged to remain on their dose of LEM for 1-week prior to titrating up to LEM10, and those assigned to LEM10 will be encouraged to remain on their dose of LEM prior to titrating down to LEM5 after one week.

Subjects who intermittently use ZOL are expected to be more likely to be started on LEM5 in the outpatient setting, as they are not chronically exposed to, or reliant upon, pharmacologic insomnia treatments. Therefore, all subjects in Cohort 1 will be started on LEM5 during the Titration Period of the Treatment Phase.

The duration of the Treatment Phase of the Core Study is set at 2 weeks, since that amount of time is deemed reasonable by expert opinion from consultation with KOLs in Sleep Medicine for subjects to decide if they wish to continue on lemborexant.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking ZOL immediate release (ZOL-IR) or extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

8.2 Secondary Objectives (revised per Amendment 01)

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking ZOL

8.3 Exploratory Objectives (revised per Amendment 01)

- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To compare nights on which an evening dose of LEM, LEM5, and LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Total Sleep Time (TST)
    - Sleep Efficiency (SE)
    - Wake After Sleep Onset (WASO)
    - Wake Bouts
- To compare the daytime after an evening dose of LEM, LEM5, and LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Sleep Bouts

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER. Adult (≥18 years) subjects are eligible for participation if they have been diagnosed with insomnia disorder per the DSM-5th Ed (American Psychiatric Association, 2014), are currently receiving ZOL as

monotherapy for insomnia, and who agree to substitute zolpidem tartrate immediate release (ZOL-IR) or ZOL-ER with LEM, regardless of the reason.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted. The Pretreatment and Treatment Phases will comprise the Core Study. The Extension Phase is described in detail in Appendix 3.

During the Screening Period, eligible subjects will continuously wear an actigraph and prospectively record the number of days ZOL is taken during the 3-week screening period using a Data Collection System. Based on ZOL use, subjects will be assigned to 1 of 2 cohorts of ZOL use frequency: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period

All subjects in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). Within Cohort 2, subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Subjects who remain eligible for the study will enter the Baseline Period, and continuously wear an actigraph during the Titration Period. (revised per Amendment 01)

Approximately 110 subjects will be screened to provide approximately 60 subjects for randomization (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 subjects in LEM5 and 20 subjects in LEM10]).

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

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

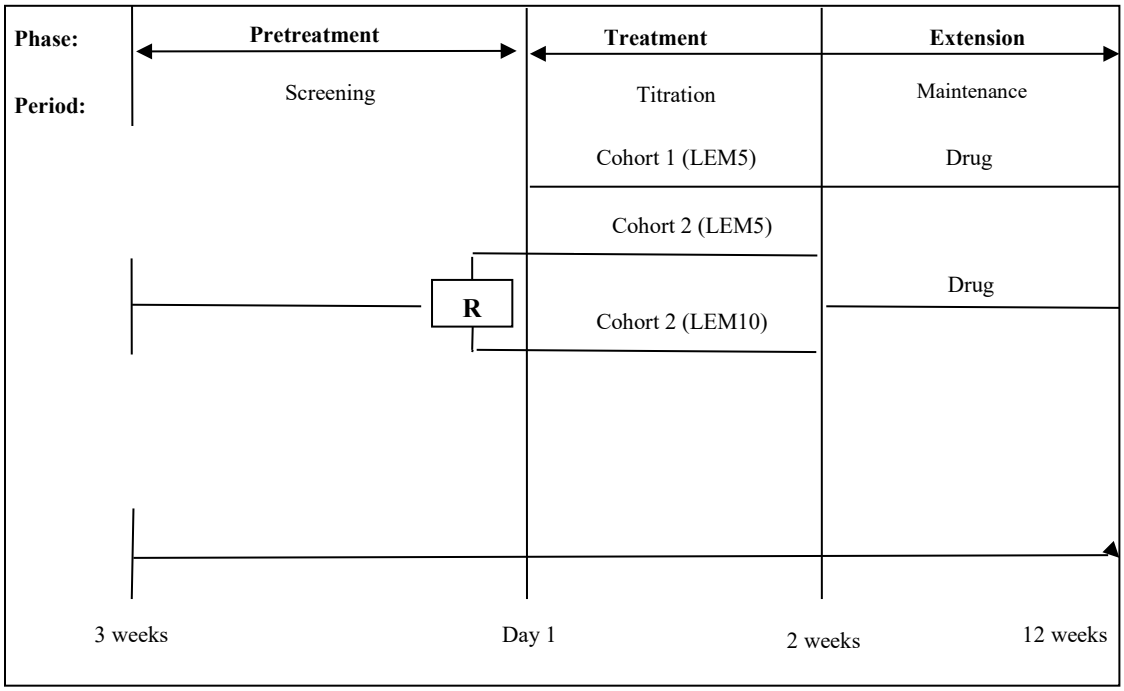

Figure 1 Study E2006-A001-312 – Study Design

LEM5 = lemborexant 5 mg, LEM5 = lemborexant 5 mg, R = Randomization

9.1.1 Pretreatment Phase (Core Study)

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

9.1.1.1 Screening Period (Core Study)

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. 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. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of insomnia per the DSM-5 (American Psychiatric Association, 2014), be currently receiving ZOL as monotherapy for insomnia, and agree to substitute zolpidem tartrate immediate release (ZOL-IR) or extended release (ZOL-ER) with LEM, regardless of the reason.

During the Screening Period, subjects will be required to bring the container of their currently prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record

the dose and frequency of ZOL which is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing this data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5 mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days of the 21-day Screening Period in order to be eligible for study inclusion. Eligible subjects will also be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period. Subjects will be provided with a daily log (sleep log) to note the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log. (revised per Amendment 01)

Subjects will return to clinic at the end of the Screening Period. Actigraph data will be downloaded and transmitted to the central reader, along with the sleep log of bedtimes, morning wake times, and the approximate times when the actigraph was replaced on the subject's wrist. (revised per Amendment 01)

For subjects who remain eligible for study enrollment, the second Screening Period visit will serve as that subject's Baseline Period, and will occur on the same day. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

9.1.1.2 Baseline Period (Core Study)

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation, return their actigraphs and sleep logs to the study site, and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible by meeting the criteria for inclusion/exclusion (Sections 9.3.1 and Section 9.3.2) will enter the Titration Period. (revised per Amendment 01)

9.1.2 Treatment Phase (Core Study)

The Treatment Phase will consist of a 2-week Titration Period and 1-day Follow-up Visit to occur 4 weeks after completion of the Titration Period (or as soon as possible following early discontinuation) for subjects not entering the Extension Phase. Subjects who meet all of the inclusion criteria and none of the exclusion criteria at the Baseline Visit, and who have entered ZOL medication use data into the Data Collection System for at least 14 of the 21-day Screening Period as specified in the Inclusion Criteria, are eligible to enter the Treatment Phase of the study.

9.1.2.1 Titration Period (Core Study)

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep. Subjects will continue to wear their actigraphs throughout the Titration Period, with the same instructions for use. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed with the subject at each visit during the Treatment and Extension Phases. Subjects will be instructed to not alter (ie break or cut) their tablets of LEM. (revised per Amendment 01)

Subjects assigned to Cohorts 1 and 2 will self-administer the study medication according to the following regimens:

- Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will decide when to take LEM according to their usual pattern, with the requirement that they take LEM at least once per week during the 2-week Titration Period. (revised per Amendment 01)
- Cohort 2 (Frequent ZOL Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For subjects starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For subjects starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the case report form (CRF).

Every morning, subjects will enter their insomnia drug use data into the data collection system and record their sleep log data, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each clinic visit except Follow-up Visit. (revised per Amendment 01)

Upon completion of the Titration Period, actigraphs will be returned to the study site, and subjects will be considered for eligibility to enter the Extension Phase (Appendix 3). (revised per Amendment 01)

9.1.2.2 Follow-Up Period

For subjects not entering the Extension Phase, the Follow-up Period will start immediately after the end of the Treatment Phase and last for 4 weeks. The purpose of the Follow-up Period is to assess adverse events and other safety parameters. Subjects will be instructed to continue insomnia management with the health-care provider who had been treating them prior to study entry, if they so desire.

9.1.3 Extension Phase

Subjects who complete the Core Study and wish to continue taking LEM will enter the 12-week Extension Phase. Subjects will continue the LEM dose and regimen established during the Titration Period; however, the dose may be titrated up or down depending on response and tolerability, per subject input and investigator judgement. For subjects who are eligible for the Extension Phase but who do not wish to continue study participation, the reason for discontinuation from the study will be recorded. At the end of the Extension Phase, the Follow-up Period will begin, and last for 4 weeks.

Details of the Extension Phase are provided in Appendix 3.

9.2 Discussion of Study Design, Including Choice of Control Groups

See Section 7.2, Study Rationale.

9.3 Selection of Study Population

Approximately 60 subjects will be enrolled at approximately 15 sites in the United States of America. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the DSM-5 criteria for Insomnia Disorder, either currently or prior to zolpidem use, as follows:

- Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
- Frequency of complaint ≥3 times per week
- Duration of complaint ≥3 months
- Associated with complaint of daytime impairment

3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month (revised per Amendment 01)
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

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

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

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

3. Any history of moderate or severe OSA
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Reports intermittent or frequent use of ZOL at Visit 1 which is not confirmed, based on review of drug use data, at Visit 2a. Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least the last 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period (revised per Amendment 01)
13. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
14. 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 (A list of prohibited concomitant medications is presented in the protocol).
15. Used any pharmacologic modality of treatment for insomnia other than ZOL, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
16. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG

17. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
18. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
19. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
20. Hypersensitivity to lemborexant or any of the excipients.
21. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
22. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
23. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
24. History of drug or alcohol dependency or abuse within approximately the last 2 years
25. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent.
26. 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.

9.4 Treatments

9.4.1 Treatment(s) Administered

The following treatments will be administered to subjects in the Core Study (Table 1).

Table 1 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
Lemborexant	5 mg	Tablet	1×5 mg tablets, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days
Lemborexant	10 mg	Tablet	1×10 mg tablet, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For Cohorts 1 and 2A (starting dose of LEM5), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For Cohort 2B (starting dose of LEM10), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the CRF.

9.4.2 Identity of Investigational Product

Lemborexant will be supplied by the sponsor in labeled containers.

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container. The sponsor will provide the study drug packaged as open-label supplies. Each subject's study drug will consist of lemborexant tablets supplied in bottles.

9.4.2.1 Chemical Name, Structural Formula of Lemborexant

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

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Based on ZOL use during the Screening Period, subjects will be assigned to 1 of 2 cohorts as shown below: (revised per Amendment 01)

- Cohort 1 (Intermittent ZOL Use): taking ZOL at least 3 but fewer than 5 nights per week, at least the last 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): taking ZOL at least 5 nights per week for at least the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will receive LEM5. Subjects in Cohort 2 will be randomized to 1 of 2 Treatment Groups: Cohort 2A (20 subjects) will start on LEM5, and Cohort 2B (20 subjects) will start on LEM10.

9.4.4 Selection of Doses in the Study

The doses to be administered are LEM5 and LEM10. In December 2018, these doses were submitted for approval in the US for the indication of insomnia. These doses were originally selected after conducting a dose-finding study (E2006-G000-201) after which their safety and efficacy were confirmed in 2 Phase 3 studies, Studies 303 and 304.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be provided a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time they intend to sleep. Subjects will be instructed on study restrictions

pertaining to duration of time spent in bed, use of alcohol, and timing of meals. Subjects will be instructed not to alter (ie, break or cut) their tablets of LEM.

9.4.6 Blinding

This is an open-label study with randomization to treatment for subjects assigned to Cohort 2.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent or 30 days before first dose/administration of study drug, if appropriate) will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study.

9.4.7.1 Drug-Drug Interactions

Coadministration with moderate and strong CYP3A inhibitors may moderately increase exposure to lemborexant, and CYP3A inducers may markedly decrease lemborexant exposure. Drug interactions with lemborexant are described in further detail in the Investigator's Brochure; prohibited concomitant medications are described in Section 9.4.7.2 and listed in Appendix 2.

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.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (Appendix 2) should not be used during the study. A subject must discontinue any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

Prohibited medications include strong and moderate CYP3A inhibitors and all CYP3A inducers. Prohibited therapies also include: any pharmacologic treatment for insomnia disorder (with the exception of ZOL use during the Screening Period only); medications that are used for the purpose of inducing sleep (hypnotics) and medications that have known sedating effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications (Appendix 2) 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 2, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. Note that strong and moderate CYP3A inhibitors and all CYP3A4 inducers will not be permitted at any time for any duration during the study.

If a subject starts any prohibited medication or a new treatment/modality for insomnia disorder, he/she must discontinue from the study.

Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study. If subjects cannot comply after counseling, they may be discharged from the study.

9.4.8 Treatment Compliance

Compliance will be assessed by examination of bottles returned to the investigator at the end of the Titration Period.

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 for the institution where the study is to be conducted

- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor. 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 [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance.

Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned

to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity.

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical, sleep, and psychiatric history will be recorded as designated in the Schedule of Procedures/Assessments (Table 3). All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations will be performed, as designated in the Schedule of Procedures/Assessments (Table 3). A full physical examination will be performed, excluding a urogenital examination unless there are special circumstances and at the discretion of the investigator. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.2.2 Sleep Drug History Questionnaire

At Screening, subjects will complete a questionnaire reporting their history and response to prior sleep medications, as well as their motivation for participating in the study.

9.5.1.2.3 Sleep Disorder Screening Battery

A lifetime history of sleep disorders will be obtained only at the 1st Screening Visit. For insomnia complaints, this history will include clinical, qualitative assessment and/or confirmation that subjects meet diagnostic criteria for insomnia disorder. The history will also include information regarding habitual sleep timing, bedtime routines, and other aspects

of sleep hygiene to determine eligibility and to exclude subjects whose insomnia symptoms appear to be due to poor sleep hygiene or to frequent napping, for example.

For the detection of other sleep disorders, the Sleep Disorders Screening Battery (SDSB) will be administered (see below).

The SDSB will include the following, to be self-administered by subjects:

- The STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA (Chung et al., 2008)
- The IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome (Abetz et al., 2006).

9.5.1.2.4 SLEEP DRUG EXPERIENCE INTERVIEW – ZOLPIDEM

At the end of the Screening Period, subjects will be asked questions about their subjective experiences while taking ZOL. The responses will be compared to the Sleep Drug Experience Interview – Lemborexant, which is done at the end of the Treatment Phase, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 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. The ISI will be completed at each study visit except Follow-up Visit.

9.5.1.3.2 PATIENT'S GLOBAL IMPRESSION – INSOMNIA

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep (Herring, et al., 2018). The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.3 QUALITY OF SLEEP RATING

The Quality of Sleep Rating (Krystal and Edinger, 2008) is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.4 SLEEP DRUG EXPERIENCE INTERVIEW – LEMBOREXANT

At the end of the Titration Period, subjects will be asked questions about their subjective experiences while taking LEM. The responses will be compared to the Sleep Drug Experience Interview – ZOL, which is done at the end of the Screening Period, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3.5 ACTIGRAPHY (REVISED PER AMENDMENT 01)

An actigraph is a device that consists of a compact, wrist-worn, battery-operated activity monitor that looks like a wrist watch. This device incorporates a multidirectional accelerometer to monitor degree and intensity of motion. Data from an actigraph are collected at a sampling rate of every 30 seconds and are scored as sleep or wake with a validated algorithm. Sleep/wake parameters are calculated from the scored data.

Eligible subjects will be provided with an actigraph (for actigraphy) to wear continuously throughout the Screening Period, and, for those who qualify at the end of the Screening Period for study enrollment, during the Treatment Phase. Subjects will be provided with a daily log (sleep log) for noting the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Subjects will be trained to use the actigraph and the log. Site staff will instruct subjects to record (with the current date) the following timings in the log: in the evening, record the times when the actigraph was not worn; and in the morning, record the bedtimes and morning rise times. Site staff will emphasize the importance of recording these timings in the log.

A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the subject.

Actigraphy data will be used to evaluate the following sleep and wake parameters for subjects during the Screening and Titration Periods:

- TST: The total time spent in sleep according to the epoch-by-epoch wake/sleep categorization during time in bed (TIB)

- SE: 100% × the total duration of sleep epochs during the defined nocturnal sleep period/TIB
- WASO: The total time spent awake according to the epoch-by-epoch wake/sleep categorization between sleep start (based on 'lights out') and 'got up'
- Wake Bouts: Wake of ≥ 5 minutes that occur during TIB
- Sleep Bouts: Continuous sleep ≥ 10 minutes that occur during Time Out of Bed (TOB)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity), regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations. Subjects will be asked about falls at every visit.

Sponsor's grading for laboratory values are presented in Appendix 1.

Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms (PTs) 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 [standard MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [faintness], and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events considered serious.

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lemborexant (in doses of 5 mg and 10 mg).

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, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase and for 7 days or 5× the half-life after the last dose, whichever is longer. SAEs will be collected for 28 days after the last dose or for 5× the half-life, whichever is longer.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

The number (percentage) of subjects with treatment emergent adverse events (TEAEs) of cataplexy or other events that are characterized according to the customized MedDRA query PT as cataplexy related events will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately.

Customized MedDRA Queries for AEs that could potentially be considered cataplexy will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. All AEs must be followed for 28 days, or 5× the half-life, whichever is longer after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

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

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

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

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

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

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

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

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

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.

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, including, cataplexy, potential cataplexy, convulsion, fall, and seizure, should always be considered adverse events and reported on the Adverse Event CRF and on the event-specific CRFs designed to collect additional information on specific events.

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

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	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Clinical laboratory tests during the Screening, Baseline, and Titration Periods will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

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

9.5.1.5.5 VITAL SIGNS, HEIGHT, AND WEIGHT MEASUREMENTS

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

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Documentation of the physical examination 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 Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

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

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

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

Columbia-Suicide Severity Rating Scale

The C-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Suicidality will be assessed as designated in the Schedule of Procedures and Assessments (Table 3), using a site-administered version of the C-SSRS (Posner, et al., 2011).

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments (Table 3).

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 3). This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, phencyclidine (PCP), opiates, benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments – Core Study

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Core Study.

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		E T[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0	2	6		
Procedures/Assessments							
Demography	X						
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Sleep Drug History Questionnaire	X						
Sleep Disorder Screening Battery[g]	X						
Insomnia Severity Index	X	X[h]	X	X		X	X
C-SSRS	X	X[h]	X	X	X	X	X
Medical, sleep, psychiatric history	X						
Prior and concomitant medications	X	X[h]	X	X	X	X	X
Dispense study drug			X	X			
Retrieve unused study drug				X		X	
Study drug compliance				X		X	X
Physical examination[i]	X	X[h]	X	X	X	X	X
Vital signs and weight	X	X[h]	X	X	X	X	X

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		E T[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0	2	6		
Procedures/Assessments							
Height	X						
Clinical laboratory tests[j]	X		X	X		X	X
Urine drug screen[k]	X	X[h]	X	X		X	X
Urine pregnancy test[l]	X	X[h]	X	X		X	X
Serum pregnancy test[l,m]	X						X
12-lead ECG[n]	X	X[h]	X	X		X	X
PGI-I[o]	X	X[h]	X	X		X	X
Quality of Sleep Rating[o]	X	X[h]	X	X		X	X
Sleep Drug Experience Interview - zolpidem		X				X	X
Sleep Drug Experience Interview - lemborexant				X			
Dispense actigraph	X						
Retrieve actigraph		X[p]		X		X	

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study (revised per Amendment 01)

Phase	**Pretreatment**			**Treatment**			
Period	**Screening**		**Baseline**	**Titration**	**Follow-Up[a]**		
Visit	**1**	**2a[b]**	**2b[b]**	**3[c]**		**E T[d,e]**	**UNS[e,f]**
Week	**-3 (Days -21 to -1)**	**-**	**0**	**2**	**6**		
Procedures/Assessments							
Review data from data collection system and sleep log		X[h]	X	X		X	X
Adverse events[q,r]	X	X[h]	X	X	X	X	X

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram, PGI-I = Patient Global Impression – Insomnia, T = Termination Visit, UNS = Unscheduled Visits
All visits to be done within ±7 days of the schedule, except for Visits 2, 3 and 4, which must be done within ±3 days.

a: The Follow-up Visit will be conducted 4 weeks after the End of Study Visit for subjects who completed the Titration Period but do not enter the Extension Phase.
b: Subjects will return to clinic at the end of the Screening Period. The Baseline Period will occur on the same day for subjects who remain eligible for study enrollment. Assessments conducted at the end of the Screening Period (Visit 2a) will serve as the assessments for the Baseline Period (Visit 2b) if a subject is enrolled into the Treatment Phase. Assessments will be performed once across Visit 2a and Visit 2b. Assessments to be conducted at Baseline (but which are not done at Visit 2a) will include clinical laboratory tests and dispensing of study drug.
c: This visit will represent the End of Study Visit for subjects who completed the Titration Period but are not entering the Extension Phase. Subjects should otherwise enter the Extension Phase immediately after completion of the Titration Period of the Core Study, in which case this visit will also serve as the first visit of the Extension Phase.
d: Subjects who discontinue study drug prematurely at any time after entering the Treatment Phase will be encouraged to return to the site as soon as practicable (preferably within 7 days) to complete the Early Termination Visit.
e: ECG will only be done during Early Termination and Unscheduled Visits if the results from the previous visit were deemed to be clinically significant by the investigator.
f: Assessments during Unscheduled Visits will be conducted at the discretion of the investigator.
g: Sleep Disorders Screening Battery comprises: STOP Bang and International Restless Legs Scale.
h: Data for Visit 2a will represent the Baseline Period (Visit 2b) assessment if the subject is enrolled. Assessments will be performed once across Visit 2a and Visit 2b.
i: A full physical examination will be conducted at Visit 1. A brief physical examination will be conducted at Visit 2a, Visit 3, and at the Follow-up Visit. For Early Termination and Unscheduled Visits, a physical examination will be conducted at the discretion of the investigator.
j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
k: Urine drug test at Unscheduled Visits will be conducted at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an AE
l: Female subjects of child-bearing potential only.
m: To be conducted at Visit 1, and if urine pregnancy testing is positive.
n: The ECG should be repeated if a clinically significant (as determined by the investigator) abnormality is observed.
o: From the beginning of the Pretreatment Phase to the end of the Treatment Phase, and provided an insomnia drug was taken the night prior, PGI-I and Sleep Quality Rating data will be entered into the electronic data capture system by the subject.
p: Actigraphs will be collected from subjects who do not meet Screening criteria after data review at Visit 2a. (revised per Amendment 01)
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 9.5.1.5, Adjudication Committee.
r: 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 its resolution. (revised per Amendment 01)

Table 5 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

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

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of nighttime sleep and daytime impairment complaints, the ISI will be evaluated for changes from baseline.

The PGI-I has been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. The C-SSRS, a standardized assessment required by regulatory authorities, will be used to evaluate any effects of lemborexant on suicidality.

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 in the Treatment Phase, 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 of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

A congenital anomaly, death during perinatal period, 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

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events—cataplexy, potential cataplexy, convulsion, fall, seizure—should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

Not applicable.

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 (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

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

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic response, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event CRF.

Sites will be assessed for the appropriateness of study drug storage and retrieval at the time of site selection. Required policies and procedures will be clearly communicated to the site to assess the site's capabilities and adherence to storage, dispensing, reconciliation, and retention of study drug.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and a snapshot of the database is obtained and released) and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. The study endpoints for efficacy and safety will presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

This study is designed to reflect clinical practice, in which patient satisfaction of the treatment after switching is an important consideration for maintaining a patient on that treatment. This was the basis for defining the outcome of transition to lemborexant. While sleep quality assessments are included as secondary outcomes in this pilot study to supplement the Phase 3 clinical trial data, it is not necessary to establish the absolute amount of improvement in sleep parameters, but rather whether the subject is satisfied enough to continue treatment with lemborexant.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses or preference to continue insomnia management with another health care provider).

9.7.1.1.2 SECONDARY ENDPOINTS (REVISED PER AMENDMENT 01)

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

9.7.1.1.3 EXPLORATORY ENDPOINTS (REVISED PER AMENDMENT 01)

The exploratory endpoints are as follows:

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment

- To compare nights on which an evening dose of LEM, LEM5, and LEM10 was taken, to nights on which an evening dose of ZOL was taken, for the following sleep-related actigraphy variables:
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- To compare the daytime after an evening dose of LEM, LEM5, and LEM10 was taken, to the daytime after an evening dose of ZOL was taken, for the following wake-related actigraphy variable:
    - Mean Duration of Sleep Bouts

9.7.1.2 Definitions of Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the FAS.

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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by randomized treatment groups.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each randomized and end of the Titration Period treatment groups using descriptive statistics. Continuous demographic variables include age, height, weight, and BMI; categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (<18.5, 18.5 to <25, 25 to ≥30), race, and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using ISI, PGI-I, and Quality of Sleep Rating.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization WHO Drug Global March 2019 or later. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by randomized treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD PT.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be conducted on the FAS. Efficacy endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan. (revised per Amendment 01)

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES (REVISED PER AMENDMENT 01)

The secondary analyses are as follows:

- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was “just right” at the end of the Titration Period (as data allow) will be reported.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES (REVISED PER AMENDMENT 01)

- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups.

- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of Titration Period dose groups.
- Average value of following sleep-related actigraphy variables will be summarized by treatment over the nights on which an evening dose of LEM, LEM5, LEM10, and ZOL was taken.
    - Mean TST
    - Mean SE
    - Mean WASO
    - Number of Wake Bouts
- Average value of wake-related actigraphy variable, mean duration of Sleep Bouts will be summarized by treatment over the daytime after an evening dose of LEM, LEM5, LEM10, and ZOL was taken.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.

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.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of AEs will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

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

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

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to a Customized MedDRA Query (CMQ) PT as cataplexy-related events, as well drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately. In addition, 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, as per the Adjudication Committee description.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and end of Titration Period dose using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

9.7.1.8.4 VITAL SIGNS

Mean changes from baseline in vital signs (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and out-of-range vital signs will be summarized by end of Titration Period dose groups for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

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 4). 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 (Safety Analysis Set), by end of Titration Period dose and time point.

Table 4 Clinically Notable Vital Sign Criteria

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

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at Screening and at the end of the Titration Period. The incidence of abnormal ECG findings will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL Use) and Cohort 2 (Frequent ZOL Use) using descriptive statistics. Shift tables will present changes from baseline in ECG interpretation (categorized as normal and abnormal) by time point.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

Urine drug test results and pregnancy test results will also be listed.

9.7.2 Determination of Sample Size

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for ZOL. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform

whether the proposed strategies are sufficient to determine whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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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 should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as Interactive Voice/Web Response System (IxRS), x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

- Electronic Patient-Reported Outcome by self-reported measures

11.4 Recording of Data

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

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

The efficacy assessments are evaluated based on the data entered into electronic Patient-Reported Outcome. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

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

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, 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 principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designated contractor, or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/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.

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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				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, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	• Barbiturates • Benzodiazepines • gamma-aminobutyric acid (GABA) analogues • Hydantoins • Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter [OTC])	• Diphenhydramine HCl • Carbinoxamine • Doxylamine • Dimenhyrinate • Triprolidine • Bromopheniramine • Chlorphenamine • Hydroxazine
Antihistamines with known sedating effects	• Non-sedating, eg, Claritin™ is not prohibited
Anxiolytics with known sedating effects	• Lorazepam • Alprazolam • Buspirone

Category	Medication
Strong CYP3A inhibitors	• Amiodarone • Bocepravir • Clarithomycin • Cobicistat • Conivaptan • Danoprevir • Diltizem • Elteravir • Fluvoxamine • Grapefruit juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telapravir • Telethromycin • Tipranavir • Troleandomycin • Voriconazole
Moderate CYP3A inhibitors	• Amprenavir • Aprepitant • Atazanavir • Casopitant • Cimetidine • Ciprofloxacin • Clotrimazole • Crizotinib • Cyclosporin • Darunavir • Dronadarone • Erythromycin • Faldaprevir • Fluconazole • Fluvoxamine • Imatinib • Netupitant • Tofisopam • Verapamil

Category	Medication
Cytochrome P450 (CYP)3A inducers	• Avasimibe • Bosentan • Carbamazepine • Efavirenz • Enzaluteamide • Etravirine • Lersivirine • Modafinil • Mitotane • Nafcillin • Phenobarbital • Phenytoin • Rifabutin • Rifampin • St John's Wort • Troglitazone • Talviraline • Thioridazine
Hypnotics	• Melatonin • Prescribed or OTC
Herbal preparations with sedating effects	• -
Monoamine oxidase inhibitors (MAOIs)	• -
Opioid Analgesics	• -
Muscle relaxants (centrally-acting) with known sedating effects	• GABA analogues • Hydantoins • Phenyltriazines
Other	• Warfarin, heparin, ticlopidine • Systemic isoretinoin • Systemic glucocorticoids

Appendix 3 Extension Phase

Study Design and Plan

The Extension Phase comprises a Maintenance Period of up to 12 weeks in duration, and a Follow-up Period visit that is to occur 4 weeks after the end of the Maintenance Period.

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of Lemborexant (LEM) that they took at the end of the Titration Period. Subjects will subsequently return to clinic at the visit as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, and study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Maintenance Period).

End of Study

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

Study Drug Supplies

Subjects will enter the Extension Phase from the Titration Phase of the Core Study, taking the same dose of LEM that was their final dose of the Titration Phase, ie, LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Schedule of Procedures/Assessments

Table 5 presents the Schedule of Procedures and Assessments for the 12-week Extension Phase.

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 – Extension (revised per Amendment 01)

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				
C-SSRS	X	X	X	X
Prior and concomitant medications	X	X	X	X
Study drug compliance	X		X	X
Dispense study drug				
Retrieve unused study drug	X		X	X
Physical examination[e]	X	X	X	X
Vital signs and weight	X	X	X	X
Clinical laboratory tests[f]	X		X	X
Urine drug screen[g]	X		X	X
Urine pregnancy test[h]	X		X	X
Serum pregnancy test[h,i]				X
12-Lead ECG[j]	X		X	X
Adverse events[k,l]	X	X	X	X

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 – Extension (revised per Amendment 01)

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram.

All visits to be done within ±7 days of the schedule.

a: The Follow-up Visit will be conducted 4 weeks after the end of the Extension Phase.
b: Subjects who discontinue study drug prematurely at any time after entering the Extension will be encouraged to return to the site as soon as practicable (preferably within 7 days).
c: During Early Termination and unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.
d: Assessments during an Unscheduled Visit to be conducted at the discretion of the investigator.
e: A full physical examination will be conducted at Visit 4 and 5 and at the Early Termination and Unscheduled Visit at the discretion of the investigator.
f: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
g: Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
h: Female subjects of child-bearing potential only.
i: To be conducted if urine pregnancy testing is positive
j: The ECG should be repeated if a clinically significant abnormality (as determined by the investigator) is observed.
k: 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 9.5.1.5, Adjudication Committee
l: If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or severe unexpected AE and at its resolution. (revised per Amendment 01)

Statistical Analyses

All statistical analyses will be the responsibility of the Biostatistics Department of Eisai. Statistical programming and analyses will be performed using SAS or other validated software.

Safety Analyses

The primary focus of data summarization for the Extension Phase will be on safety and tolerability. Evaluations of safety data will be performed on the Safety Analysis Set.

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-312

Study Protocol Title: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia

Investigational Product Name: E2006\Lemborexant

IND Number: 111871

SIGNATURES

Authors:

PPD

Eisai, Inc

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Investigational Product Name:	E2006\Lemborexant
IND Number:	111871

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International 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.

<Name of institution>

Medical Institution

<Name, degree(s)>		
Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 1.0

New version /date: Version 2.0/12 Apr 2019

Change	Rationale	Affected Protocol Sections
Modified the text in Exclusion Criterion No. 1 to replace urine pregnancy test with serum pregnancy test.	Administrative change	• Synopsis –Exclusion criteria • Section 9.3.2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	E2006/Lemborexant
Indication:	Insomnia
Phase:	3b
	V1.0 12 Apr 2019 (original protocol)
	V2.0 12 Apr 2019 (revised original protocol)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
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2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Pilot Study to Evaluate Next-Dose Transition From Zolpidem to Lemborexant for the Treatment of Insomnia

Investigator(s)

Unknown

Sites

Approximately 15 sites within the United States of America

Study Period and Phase of Development

Phase 3b pilot study

Estimated duration of up to 38 weeks from first subject in to last subject's last visit.

Objectives

Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking zolpidem tartrate immediate release (ZOL-IR) or zolpidem tartrate extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

Secondary Objectives

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking zolpidem (ZOL)

Exploratory Objective(s)

None

Study Design

E2006-A001-312 is a multicenter Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. The Pretreatment and Treatment Phases will comprise the Core Study. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted.

Core Study

Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

Screening Period

During the Screening Period, subjects will be required to bring the container of their prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the frequency of ZOL is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing these data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days out of the allowable 21-day Screening Period in order to be eligible for study inclusion.

Subjects will return to clinic at the end of the Screening Period. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Baseline Periody

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible will enter the Titration Period.

Treatment Phase

Titration Period

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep at night. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed. Subjects will be instructed to not alter (ie, break or cut) their tablets of LEM.

Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will determine the nights on which they take LEM, with the requirement that they take LEM at least once per week during the 14–day Titration Period.

Cohort 2 (Frequent Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.
For subjects with a starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site should they feel that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
For subjects with a starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site should they feel that LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.
At the time of LEM dose change during the Core Study, the reason for the dose change will be recorded in the case report form (CRF). Subjects will be allowed 1 LEM dose adjustment during the Titration Period. Every morning, subjects will enter their insomnia drug use data into the data collection system, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating. The ISI will be completed at each study visit except Follow-up Visit. .
Upon completion of the Titration Period, subjects will be eligible to enter the Extension Phase.

Extension Phase

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of LEM that they took at the end of the Titration Period. Subjects will subsequently return to clinic as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Treatment Phase for subjects not entering the Extension Phase or after the end of the Extension Phase, for subjects entering the Extension Phase).

End of Study

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

Number of Subjects

Approximately 110 subjects will be screened to provide approximately 60 subjects (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 in LEM5, 20 in LEM10]).

Inclusion Criteria

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) criteria for Insomnia Disorder, either currently or prior to ZOL use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

Exclusion Criteria

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

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

dosing).

3. Any history of moderate or severe obstructive sleep apnea (OSA)
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
13. 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 (A list of prohibited concomitant medications is presented in the protocol).
14. Used any pharmacologic modality of treatment for insomnia other than zolpidem, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
15. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
16. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
17. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
18. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
19. Hypersensitivity to lemborexant or any of the excipients.
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
21. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
22. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years

23. History of drug or alcohol dependency or abuse within approximately the last 2 years
24. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent
25. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Core Study

Test drug:

LEM5 or LEM10 taken orally in tablet form at night within a few minutes of the time the subject intends to sleep, according to the subject's predetermined intermittent or frequent use schedule.

Comparator Drug: Not applicable

Extension Phase

Test drug:

LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Duration of Treatment

A maximum of 14 weeks:

2 weeks of LEM5 and/or LEM10 during the Treatment Phase of the Core Study,

12 weeks during the Extension Phase

Concomitant Drug/Therapy

Prohibited medications should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Phase.

Prohibited medications include moderate and strong cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers, and medications that have known sedating effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study. Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study.

Assessments

Screening Assessments (Core Study only)

Sleep Disorders Screening Battery (SDSB):

The SDSB will include:

- STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA
- IRLS: a subjective scale comprising 10 questions, which measures severity of symptoms of restless legs syndrome

Sleep Drug History Questionnaire

Subjects will be asked questions about their history and response to prior sleep medications.

Sleep Drug Experience Interview – Zolpidem

Subjects will be asked questions about their subjective experiences while taking ZOL at the end of the Screening Period.

Efficacy Assessments (Core Study only)

Patient Global Impression – Insomnia

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep. The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening.

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. The ISI will be completed at each study visit except Follow-up Visit.

Quality of Sleep Rating

The Quality of Sleep Rating is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

Sleep Drug Experience Interview – Lemborexant

Subjects will be asked questions about their subjective experiences while taking LEM at the end of the Titration Period.

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments (Core Study and Extension Phase)

Safety assessments will consist of monitoring and recording all adverse events (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. Subjects will be asked about falls at every visit.

Adjudication Committee

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

Columbia – Suicide Severity Rating Scale

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

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments.

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments. This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, PCP, opiates, benzodiazepines, barbiturates, and amphetamines.

Bioanalytical Methods

Not applicable.

Statistical Methods

The study endpoints for efficacy and safety will be presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed.

Primary Endpoint

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses, or preference to continue insomnia management with another health care provider).

Secondary Endpoints

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.

Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the Full Analysis Set.

Efficacy Analyses (Core Study only)

All efficacy analyses will be conducted on the FAS.

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.
- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall,
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of the Titration Period dose groups.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses (Core Study and Extension Phase)

Evaluations of safety data will be performed on the SAS.
The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical

laboratory variables, and vital signs will be summarized for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics using end of titration dose group. AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.
Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and PTs related to drug abuse liability, will be summarized seperately. The results of the deliberation of the Adjudication Committee will be reported separately.
In addition, 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, as per the Adjudication Committee description.

Other Analyses (Core Study)

Primary and secondary endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan.

Interim Analyses

No interim analyses are planned for this study.

Sample Size Rationale

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for zolpidem. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to evaluate whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BMI	Body mass index
BP	blood pressure
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed
FAS	full analysis set
GABA	gamma-aminobutyric acid
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISI	Insomnia Severity Index
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
LEM	lemborexant
LEM5	Lemborexant 5 mg
LEM10	Lemborexant 10 mg
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
OSA	obstructive sleep apnea
PBO	placebo
PGI-I	Patient Global Impression of Insomnia
PT	preferred term
QTcF	Difference between QTc corrected by Fridericia's formulas
SAE	Serious adverse events
SAS	safety analysis set
SDSB	Sleep Disorders Screening Battery
SOC	system organ class
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
ZOL	zolpidem
ZOL-ER	zolpidem tartrate extended release
ZOL-IR	zolpidem tartrate immediate release

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Title 21 of the United States Code of Federal Regulations [CFRs], Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate CRA[s], change of telephone number[s]). Documentation of IRB compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

Study progress is to be reported to IRBs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports, and inform the IRB of any reportable adverse events (AEs) per ICH guidelines and local IRB/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 within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB 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 (2013)
- ICH E6 Guideline for GCP (Committee for Proprietary Medicinal Products [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 US CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

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

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

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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 15 investigational sites in the United States of America.

The name, telephone and fax numbers of the Medical Monitor and other contact personnel at the contract research organization(s) (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Indication

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

7.1.1 Current Therapeutic Options

Treatments for insomnia include both non-pharmacological (Schutte-Rodin, et al., 2008; Morgenthaler, et al., 2006) and pharmacological treatments (Sateia, et al., 2017). Patients who undergo thorough diagnostic evaluations for insomnia symptoms are asked about their sleep and wake habits, since some cases of insomnia can be addressed by improving sleep hygiene. Principles of good sleep hygiene include regular bedtimes and waketimes, limiting alerting activities before bedtime, and limiting caffeine and alcohol intake, among others (Schutte-Rodin, et al., 2008). These techniques are often not adequate to address insomnia symptoms (Stepanski and Wyatt, 2003; Irish, et al., 2015).

Another commonly recommended non-pharmacological approach is the use of cognitive behavioral therapy for insomnia (CBT-I; Schutte-Rodin, et al., 2008). CBT-I includes techniques to minimize wakefulness at the time the patient intends to sleep. However, while there are data to support the effectiveness of CBT-I, sleep restriction is commonly a major component, and this may lead to daytime sleepiness, an unintended consequence of short sleep (Kyle, et al., 2014). In contrast, lemborexant's mechanism of action would avoid the daytime sleepiness caused by sleep restriction, while reducing wakefulness and facilitating sleep, which is an important underlying goal of CBT-I.

There are numerous drugs available for the treatment of insomnia, some available by prescription and many available over-the-counter. Many of the over-the-counter medicines lack empirical data from adequate, well-designed and controlled clinical trials to support their use (Rosen, et al., 2005); these include melatonin and antihistamines. Pharmacological treatments available by prescription and used clinically for insomnia include sedative hypnotics (benzodiazepines, nonbenzodiazepine gamma-aminobutyric acid (GABA)-releasing [GABAergics] agents), sedating antidepressants, melatonin agonists, and a DORA.

7.1.2 Lemborexant

Lemborexant belongs to the pharmacologic class of orexin receptor antagonists, a class of chemical compounds developed for the treatment for insomnia. To date, clinical proof of concept has been achieved by 6 orexin receptor antagonists (lemborexant, almorexant [ACT-078573], suvorexant [MK-4305], filorexant [MK-6096]), seltorexant [MIN-202], and nemorexant [ACT-541468]), demonstrating validity of the mechanism of action (Herring, et al., 2012; Hoever, et al., 2012; Connor, et al., 2016; Murphy, et al., 2017; De Boer, et al., 2018).

Nonclinical data show that lemborexant binds to and competitively antagonizes human orexin-1 receptor (OX1R) and orexin-1 receptor (OX2R) in vitro, with rapid association and dissociation kinetics at both receptors. In vitro data show that lemborexant does not substantially interact with other sleep-related receptors and channels (Beuckmann, et al, 2017). Lemborexant prevents [Ala^{11}, D-Leu^{15}]-orexin-B-induced plasma adrenocorticotropic hormone increase in rats, and promotes physiological sleep in mice and rats. In mice, lemborexant does not promote sleep when the orexin pathway has been functionally impaired. In rats, daily treatment for 3 consecutive weeks with lemborexant did not result in tolerance or wakefulness rebound upon treatment cessation, and did not elicit direct transitions from wakefulness to rapid eye movement (REM) sleep, a narcolepsy-like symptom. However, in strong emotional contexts, lemborexant induced cataplexy-like events in mice (Study W-20140712). Cataplexy has been noted in dogs dosed with another orexin antagonist, suvorexant, when presented with food enrichment (Belsomra, 2018), but the relationship to cataplexy symptoms in humans has not been established. At doses up to 300 mg/kg (300-fold higher than necessary for sleep promotion), lemborexant did not have any negative influence on motor coordination in mice, nor did it show any significant interaction with ethanol.

7.1.2.1 Clinical Experience With Lemborexant

The safety and efficacy of lemborexant for the treatment of insomnia disorder was confirmed in 2 pivotal Phase 3 studies, E2006-G000-303 (Study 303) and E2006-G000-304 (Study 304). In Study 304, lemborexant also demonstrated superior improvement on objective and subjective measures of sleep onset and maintenance compared to zolpidem tartrate extended release (ZOL-ER). Additional safety assessments pertinent to insomnia drugs, specifically regarding postural stability, were also conducted in study E2006-A001-108 and Study 304. In these studies, the safety of lemborexant on postural stability was superior compared to zolpidem (ZOL). Based on these data, a New Drug Application for lemborexant was submitted to the US Food and Drug Administration for the treatment of insomnia disorder in December 2018 and accepted for review in February 2019.

The safety and tolerability of lemborexant has been comprehensively evaluated in a broad patient population that includes subjects with insomnia disorder per Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) (with or without medical or psychiatric comorbidities), subjects with Alzheimer's disease and ISWRD, subjects with mild obstructive sleep apnea (OSA), and subjects with severe renal impairment or mild to

moderate hepatic impairment. Exposures included dosing of ≥12 months. Approximately 40% of subjects in the development program were elderly (≥65 years), providing extensive safety and tolerability profile for this important subpopulation at risk for insomnia.

Overall, of 2824 subjects with sleep disorders, 1848 received lemborexant, 714 received placebo (PBO), and 263 received ZOL.

No deaths were reported in subjects treated with lemborexant.

The overall incidence of treatment-emergent serious adverse events (SAEs) for subjects treated with lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10) in the Phase 3 Pool was low (2.8% and 2.3%, respectively) but greater than for PBO (0.9%). However, when adjusted by duration of exposure, the overall incidence (subjects per patient-year) was similar to PBO (<0.1 for PBO, 0.1 for LEM5, and 0.1 for LEM10). The overall rate (events per patient-year) of treatment-emergent SAEs when adjusted by duration of exposure was <0.1 for PBO, <0.1 for LEM5, and <0.1 for LEM10.

There were no differences in the types of treatment-emergent SAEs reported during long-term treatment with lemborexant. There were no differences in treatment-emergent SAEs based on intrinsic factors, including age, sex, and body mass index (BMI) of subjects. Notably, the incidence of treatment-emergent SAEs in the elderly was consistent with that in younger subjects.

Across the Phase 3 studies of 303 and 304 (total subjects=1945), the majority of treatment-emergent SAEs occurred as singular events in 1 subject only. The SAEs of osteoarthritis (0% for PBO, 0.1% for LEM5, 0.4% for LEM10), rib fracture (0.2% for PBO, 0% for LEM5, 0.1% for LEM10), and diabetic neuropathy (0% for PBO, 0.3% for LEM5, 0% for LEM10) occurred in more than 1 subject across the PBO, LEM5, and LEM10 groups. One (0.1%) serious event of fall was reported in the LEM5 group.

7.1.2.2 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

None.

7.2 Study Rationale

Switching of medications for insomnia occurs often in clinical practice based on clinical response, AEs, reimbursement patterns, or physician and patient preference. However, there is no clinical trial experience or dosing guidance for transitioning from currently approved treatments for insomnia to lemborexant. Study E2006-A001-312 (Study 312) is designed as a pilot study to assess the dosing approach of directly transitioning from ZOL, the most commonly prescribed sleep aid (Bertisch, et al., 2014), to lemborexant, without tapering the ZOL dose, and with the opportunity for lemborexant dose titration. This study will provide initial information on patient satisfaction after switching to lemborexant, with secondary objectives assessing subjective quality of sleep and tolerability. If issues are identified

regarding patient satisfaction, tolerability, or quality of sleep, other dosing paradigms can be assessed in future studies to mitigate these issues.

7.2.1 Entry Criteria Rationale

Subjects with insomnia disorder per DSM-5 criteria (with or without medical or psychiatric comorbidities) will be eligible for study entry, which is representative of the typical target outpatient population. All subjects who are willing to substitute ZOL with LEM, regardless of the reason(s), will be eligible, and the reason(s) will be captured during screening. While it is anticipated that most eligible subjects would substitute ZOL with LEM due to dissatisfaction with ZOL, other reasons, as determined by input from Key Opinion Leaders (KOLs) in Sleep Medicine, may include, but are not limited to, concerns regarding ZOL side effects, eg, parasomnias. Including subjects with these various reasons is representative of the real-world outpatient setting.

While the approved dosing instructions for women and patients ≥65 stipulate that the lower dose of ZOL is to be prescribed, many women and elderly patients may be taking the higher dose. Therefore, for generalizability of the results of the study to the patient population, any stable dosing regimen will be eligible, including those subjects taking higher than approved doses up to the maximum approved (10 mg IR or 12.5 mg ER).

7.2.2 Rationale for Titration Schedule and Duration

Since this study is designed to reflect common clinical practice, flexibility to titrate the dose up or down is built into the dosing regimen. In the outpatient setting, clinicians typically advise patients to allow themselves one week to adjust to a new medication; therefore, subjects assigned to LEM5 will be encouraged to remain on their dose of LEM for 1-week prior to titrating up to LEM10, and those assigned to LEM10 will be encouraged to remain on their dose of LEM prior to titrating down to LEM5 after one week.

Subjects who intermittently use ZOL are expected to be more likely to be started on LEM5 in the outpatient setting, as they are not chronically exposed to, or reliant upon, pharmacologic insomnia treatments. Therefore, all subjects in Cohort 1 will be started on LEM5 during the Titration Period of the Treatment Phase.

The duration of the Treatment Phase of the Core Study is set at 2 weeks, since that amount of time is deemed reasonable by expert opinion from consultation with KOLs in Sleep Medicine for subjects to decide if they wish to continue on lemborexant.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking ZOL immediate release (ZOL-IR) or extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

8.2 Secondary Objectives

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking ZOL

8.3 Exploratory Objective(s)

None

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER. Adult (≥18 years) subjects are eligible for participation if they have been diagnosed with insomnia disorder per the DSM-5th Ed (American Psychiatric Association, 2014), are currently receiving ZOL as monotherapy for insomnia, and who agree to substitute zolpidem tartrate immediate release (ZOL-IR) or ZOL-ER with LEM, regardless of the reason.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted. The Pretreatment and Treatment Phases will comprise the Core Study. The Extension Phase is described in detail in Appendix 3.

During the Screening Period, eligible subjects will prospectively record the number of days ZOL is taken over 21 days using a Data Collection System. Based on these data, subjects will be assigned to 1 of 2 cohorts of ZOL use frequency:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). Within Cohort 2, subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Subjects who remain eligible for the study will enter the Baseline Period.

Approximately 110 subjects will be screened to provide approximately 60 subjects for randomization (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 subjects in LEM5 and 20 subjects in LEM10]).

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

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

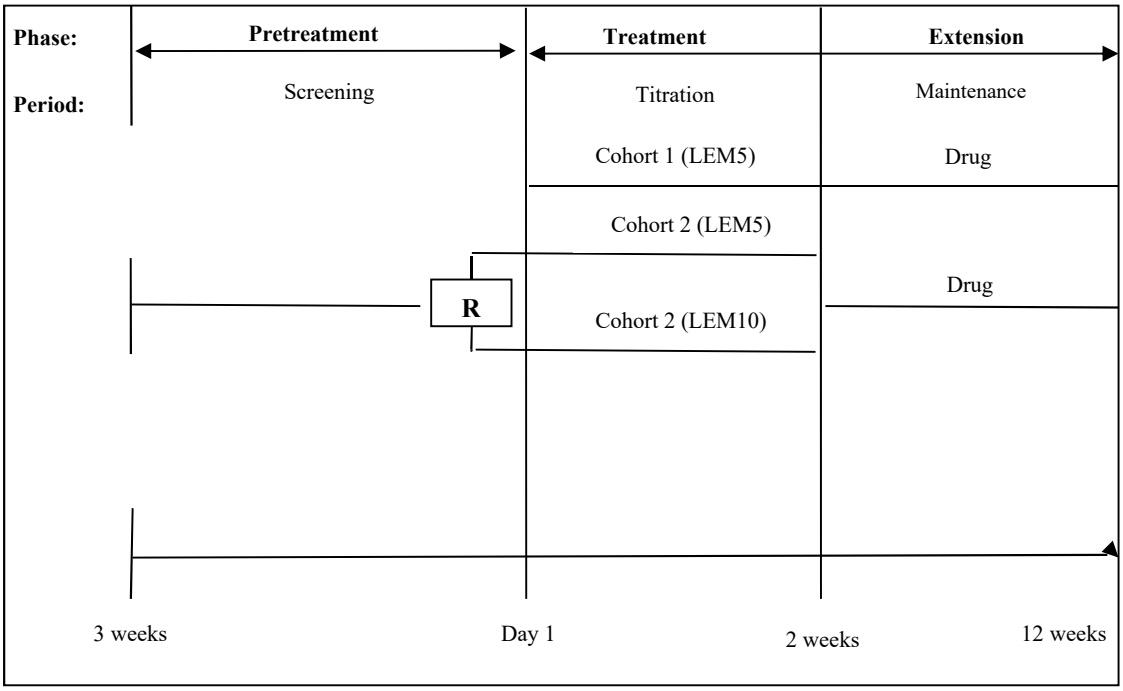

Figure 1 Study E2006-A001-312 – Study Design

LEM5 = lemborexant 5 mg, LEM5 = lemborexant 5 mg, R = Randomization

9.1.1 Pretreatment Phase (Core Study)

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

9.1.1.1 Screening Period (Core Study)

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. 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. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of insomnia per the DSM-5 (American Psychiatric Association, 2014), be currently receiving ZOL as monotherapy for insomnia, and agree to substitute zolpidem tartrate immediate release (ZOL-IR) or extended release (ZOL-ER) with LEM, regardless of the reason.

During the Screening Period, subjects will be required to bring the container of their currently prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the dose and frequency of ZOL which is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing this data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5 mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days of the 21-day Screening Period in order to be eligible for study inclusion.

Subjects will return to clinic at the end of the Screening Period. For subjects who remain eligible for study enrollment, the second Screening Period visit will serve as that subject's Baseline Period, and will occur on the same day. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

9.1.1.2 Baseline Period (Core Study)

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible by meeting the criteria for inclusion/exclusion (Sections 9.3.1 and Section 9.3.2) will enter the Titration Period.

9.1.2 Treatment Phase (Core Study)

The Treatment Phase will consist of a 2-week Titration Period and 1-day Follow-up Visit to occur 4 weeks after completion of the Titration Period (or as soon as possible following early discontinuation) for subjects not entering the Extension Phase. Subjects who meet all of the inclusion criteria and none of the exclusion criteria at the Baseline Visit, and who have entered ZOL medication use data into the Data Collection System for at least 14 of the 21-day Screening Period as specified in the Inclusion Criteria, are eligible to enter the Treatment Phase of the study.

9.1.2.1 Titration Period (Core Study)

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed with the subject at each visit during the Treatment and Extension Phases. Subjects will be instructed to not alter (ie break or cut) their tablets of LEM.

Subjects assigned to Cohorts 1 and 2 will self-administer the study medication according to the following regimens:

- Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will determine the nights on which they take LEM, with the requirement that they take LEM at least once per week during the 2-week Titration Period.
- Cohort 2 (Frequent ZOL Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For subjects starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For subjects starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10

should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the case report form (CRF).

Every morning, subjects will enter their insomnia drug use data into the data collection system, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each clinic visit except Follow-up Visit.

Upon completion of the Titration Period, subjects may be eligible to enter the Extension Phase (Appendix 3).

9.1.2.2 Follow-Up Period

For subjects not entering the Extension Phase, the Follow-up Period will start immediately after the end of the Treatment Phase and last for 4 weeks. The purpose of the Follow-up Period is to assess adverse events and other safety parameters. Subjects will be instructed to continue insomnia management with the health-care provider who had been treating them prior to study entry, if they so desire.

9.1.3 Extension Phase

Subjects who complete the Core Study and wish to continue taking LEM will enter the 12-week Extension Phase. Subjects will continue the LEM dose and regimen established during the Titration Period; however, the dose may be titrated up or down depending on response and tolerability, per subject input and investigator judgement. For subjects who are eligible for the Extension Phase but who do not wish to continue study participation, the reason for discontinuation from the study will be recorded. At the end of the Extension Phase, the Follow-up Period will begin, and last for 4 weeks.

Details of the Extension Phase are provided in Appendix 3.

9.2 Discussion of Study Design, Including Choice of Control Groups

See Section 7.2, Study Rationale.

9.3 Selection of Study Population

Approximately 60 subjects will be enrolled at approximately 15 sites in the United States of America. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the DSM-5 criteria for Insomnia Disorder, either currently or prior to zolpidem use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 or 4 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

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

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

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

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

3. Any history of moderate or severe OSA
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
13. 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 (A list of prohibited concomitant medications is presented in the protocol).
14. Used any pharmacologic modality of treatment for insomnia other than ZOL, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
15. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
16. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
17. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)

18. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
19. Hypersensitivity to lemborexant or any of the excipients.
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
21. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
22. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
23. History of drug or alcohol dependency or abuse within approximately the last 2 years
24. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent.
25. 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.

9.4 Treatments

9.4.1 Treatment(s) Administered

The following treatments will be administered to subjects in the Core Study (Table 1).

Table 1 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
Lemborexant	5 mg	Tablet	1×5 mg tablets, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days
Lemborexant	10 mg	Tablet	1×10 mg tablet, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For Cohorts 1 and 2A (starting dose of LEM5), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For Cohort 2B (starting dose of LEM10), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the CRF.

9.4.2 Identity of Investigational Product

Lemborexant will be supplied by the sponsor in labeled containers.

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container. The sponsor will provide the study drug packaged as open-label supplies. Each subject's study drug will consist of lemborexant tablets supplied in bottles.

9.4.2.1 Chemical Name, Structural Formula of Lemborexant

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

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Based on ZOL use during the Screening Period, subjects will be assigned to 1 of 2 cohorts as shown below:

- Cohort 1 (Intermittent ZOL Use): taking ZOL at least 3 but fewer than 5 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will receive LEM5. Subjects in Cohort 2 will be randomized to 1 of 2 Treatment Groups: Cohort 2A (20 subjects) will start on LEM5, and Cohort 2B (20 subjects) will start on LEM10.

9.4.4 Selection of Doses in the Study

The doses to be administered are LEM5 and LEM10. In December 2018, these doses were submitted for approval in the US for the indication of insomnia. These doses were originally selected after conducting a dose-finding study (E2006-G000-201) after which their safety and efficacy were confirmed in 2 Phase 3 studies, Studies 303 and 304.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be provided a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time they intend to sleep. Subjects will be instructed on study restrictions

pertaining to duration of time spent in bed, use of alcohol, and timing of meals. Subjects will be instructed not to alter (ie, break or cut) their tablets of LEM.

9.4.6 Blinding

This is an open-label study with randomization to treatment for subjects assigned to Cohort 2.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent or 30 days before first dose/administration of study drug, if appropriate) will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study.

9.4.7.1 Drug-Drug Interactions

Coadministration with moderate and strong CYP3A inhibitors may moderately increase exposure to lemborexant, and CYP3A inducers may markedly decrease lemborexant exposure. Drug interactions with lemborexant are described in further detail in the Investigator's Brochure; prohibited concomitant medications are described in Section 9.4.7.2 and listed in Appendix 2.

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.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (Appendix 2) should not be used during the study. A subject must discontinue any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

Prohibited medications include strong and moderate CYP3A inhibitors and all CYP3A inducers. Prohibited therapies also include: any pharmacologic treatment for insomnia disorder (with the exception of ZOL use during the Screening Period only); medications that are used for the purpose of inducing sleep (hypnotics) and medications that have known sedating effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications (Appendix 2) 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 2, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. Note that strong and moderate CYP3A inhibitors and all CYP3A4 inducers will not be permitted at any time for any duration during the study.

If a subject starts any prohibited medication or a new treatment/modality for insomnia disorder, he/she must discontinue from the study.

Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study. If subjects cannot comply after counseling, they may be discharged from the study.

9.4.8 Treatment Compliance

Compliance will be assessed by examination of bottles returned to the investigator at the end of the Titration Period.

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 for the institution where the study is to be conducted

- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor. 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 [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance.

Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned

to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity.

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical, sleep, and psychiatric history will be recorded as designated in the Schedule of Procedures/Assessments (Table 3). All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations will be performed, as designated in the Schedule of Procedures/Assessments (Table 3). A full physical examination will be performed, excluding a urogenital examination unless there are special circumstances and at the discretion of the investigator. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.2.2 Sleep Drug History Questionnaire

At Screening, subjects will complete a questionnaire reporting their history and response to prior sleep medications, as well as their motivation for participating in the study.

9.5.1.2.3 Sleep Disorder Screening Battery

A lifetime history of sleep disorders will be obtained only at the 1st Screening Visit. For insomnia complaints, this history will include clinical, qualitative assessment and/or confirmation that subjects meet diagnostic criteria for insomnia disorder. The history will also include information regarding habitual sleep timing, bedtime routines, and other aspects

of sleep hygiene to determine eligibility and to exclude subjects whose insomnia symptoms appear to be due to poor sleep hygiene or to frequent napping, for example.

For the detection of other sleep disorders, the Sleep Disorders Screening Battery (SDSB) will be administered (see below).

The SDSB will include the following, to be self-administered by subjects:

- The STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA (Chung et al., 2008)
- The IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome (Abetz et al., 2006).

9.5.1.2.4 SLEEP DRUG EXPERIENCE INTERVIEW – ZOLPIDEM

At the end of the Screening Period, subjects will be asked questions about their subjective experiences while taking ZOL. The responses will be compared to the Sleep Drug Experience Interview – Lemborexant, which is done at the end of the Treatment Phase, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 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. The ISI will be completed at each study visit except Follow-up Visit.

9.5.1.3.2 PATIENT'S GLOBAL IMPRESSION – INSOMNIA

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep (Herring, et al., 2018). The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.3 QUALITY OF SLEEP RATING

The Quality of Sleep Rating (Krystal and Edinger, 2008) is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.4 SLEEP DRUG EXPERIENCE INTERVIEW – LEMBOREXANT

At the end of the Titration Period, subjects will be asked questions about their subjective experiences while taking LEM. The responses will be compared to the Sleep Drug Experience Interview – ZOL, which is done at the end of the Screening Period, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity), regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations. Subjects will be asked about falls at every visit.

Sponsor's grading for laboratory values are presented in Appendix 1.

Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms (PTs) 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 [standard MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [faintness], and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events considered serious.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lemborexant (in doses of 5 mg and 10 mg).

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, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase and for 7 days or 5× the half-life after the last dose, whichever is longer. SAEs will be collected for 28 days after the last dose or for 5× the half-life, whichever is longer.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

The number (percentage) of subjects with treatment emergent adverse events (TEAEs) of cataplexy or other events that are characterized according to the customized MedDRA query PT as cataplexy related events will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately.

Customized MedDRA Queries for AEs that could potentially be considered cataplexy will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. All AEs must be followed for 28 days, or 5× the half-life, whichever is longer after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

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

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

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

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

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

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

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

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed 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.

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, including, cataplexy, potential cataplexy, convulsion, fall, and seizure, should always be considered adverse events and reported on the Adverse Event CRF and on the event-specific CRFs designed to collect additional information on specific events.

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

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	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Clinical laboratory tests during the Screening, Baseline, and Titration Periods will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

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

9.5.1.5.5 Vital Signs, Height, and Weight Measurements

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

9.5.1.5.6 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Documentation of the physical examination 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 Adverse Events CRF.

9.5.1.5.7 Electrocardiograms

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

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

9.5.1.5.8 Other Safety Assessments

Columbia-Suicide Severity Rating Scale

The C-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Suicidality will be assessed as designated in the Schedule of Procedures and Assessments (Table 3), using a site-administered version of the C-SSRS (Posner, et al., 2011).

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments (Table 3).

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 3). This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, phencyclidine (PCP), opiates, benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments – Core Study

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Core Study.

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		ET[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0	2	6		
Procedures/Assessments							
Demography	X						
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Sleep Drug History Questionnaire	X						
Sleep Disorder Screening Battery[g]	X						
Insomnia Severity Index	X	X	X	X		X	X
C-SSRS	X	X[h]	X	X	X	X	X
Medical, sleep, psychiatric history	X						
Prior and concomitant medications	X	X	X	X	X	X	X
Dispense study drug			X	X			
Retrieve unused study drug				X		X	
Study drug compliance				X		X	X
Physical examination[i]	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X
Height	X						

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		ET[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0	2	6		
Procedures/Assessments							
Clinical laboratory tests[j]	X		X	X		X	X
Urine drug screen[k]	X	X	X	X		X	X
Urine pregnancy test[l]	X	X	X	X		X	X
Serum pregnancy test[l,m]	X						X
12-lead ECG[n]	X	X	X	X		X	X
PGI-I[o]	X	X[h]	X	X		X	X
Quality of Sleep Rating[o]	X	X[h]	X	X		X	X
Sleep Drug Experience Interview - zolpidem		X				X	X
Sleep Drug Experience Interview - lemborexant				X			
Adverse events[p]	X	X	X	X	X	X	X

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		E T[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0	2	6		
Procedures/Assessments							

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram, PGI-I = Patient Global Impression – Insomnia, T = Termination Visit, UNS = Unscheduled Visits
All visits to be done within ±7 days of the schedule, except for Visits 2, 3 and 4, which must be done within ±3 days.

a: The Follow-up Visit will be conducted 4 weeks after the End of Study Visit for subjects who completed the Titration Period but do not enter the Extension Phase.
b: Subjects will return to clinic at the end of the Screening Period. The Baseline Period will occur on the same day for subjects who remain eligible for study enrollment. Assessments conducted at the end of the Screening Period (Visit 2a) will serve as the assessments for the Baseline Period (Visit 2b) if a subject is enrolled into the Treatment Phase. Assessments will be performed once across Visit 2a and Visit 2b. Assessments to be conducted at Baseline (but which are not done at Visit 2a) will include clinical laboratory tests and dispensing of study drug.
c: This visit will represent the End of Study Visit for subjects who completed the Titration Period but are not entering the Extension Phase. Subjects should otherwise enter the Extension Phase immediately after completion of the Titration Period of the Core Study, in which case this visit will also serve as the first visit of the Extension Phase.
d: Subjects who discontinue study drug prematurely at any time after entering the Treatment Phase will be encouraged to return to the site as soon as practicable (preferably within 7 days) to complete the Early Termination Visit.
e: ECG will only be done during Early Termination and Unscheduled Visits if the results from the previous visit were deemed to be clinically significant by the investigator.
f: Assessments during Unscheduled Visits will be conducted at the discretion of the investigator.
g: Sleep Disorders Screening Battery comprises: STOP Bang and International Restless Legs Scale.
h: Data for Visit 2a will represent the Baseline Period (Visit 2b) assessment if the subject is enrolled. Assessments will be performed once across Visit 2a and Visit 2b.
i: A full physical examination will be conducted at Visit 1. A brief physical examination will be conducted at Visit 2a, Visit 3, and at the Follow-up Visit. For Early Termination and Unscheduled Visits, a physical examination will be conducted at the discretion of the investigator.
j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
k: Urine drug test at Unscheduled Visits will be conducted at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
l: Female subjects of child-bearing potential only.
m: To be conducted at Visit 1, and if urine pregnancy testing is positive.
n: The ECG should be repeated if a clinically significant (as determined by the investigator) abnormality is observed.
o: From the beginning of the Pretreatment Phase to the end of the Treatment Phase, and provided an insomnia drug was taken the night prior, PGI-I and Sleep Quality Rating data will be entered into the electronic data capture system by the subject.
p: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per Section 9.5.1.5, Adjudication Committee.

Table 5 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

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

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of nighttime sleep and daytime impairment complaints, the ISI will be evaluated for changes from baseline.

The PGI-I has been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. The C-SSRS, a standardized assessment required by regulatory authorities, will be used to evaluate any effects of lemborexant on suicidality.

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 in the Treatment Phase, 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 of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

A congenital anomaly, death during perinatal period, 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

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events—cataplexy, potential cataplexy, convulsion, fall, seizure—should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

Not applicable.

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 (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

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

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic response, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event CRF.

Sites will be assessed for the appropriateness of study drug storage and retrieval at the time of site selection. Required policies and procedures will be clearly communicated to the site to assess the site's capabilities and adherence to storage, dispensing, reconciliation, and retention of study drug.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and a snapshot of the database is obtained and released) and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. The study endpoints for efficacy and safety will presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

This study is designed to reflect clinical practice, in which patient satisfaction of the treatment after switching is an important consideration for maintaining a patient on that treatment. This was the basis for defining the outcome of transition to lemborexant. While sleep quality assessments are included as secondary outcomes in this pilot study to supplement the Phase 3 clinical trial data, it is not necessary to establish the absolute amount of improvement in sleep parameters, but rather whether the subject is satisfied enough to continue treatment with lemborexant.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses or preference to continue insomnia management with another health care provider).

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.

9.7.1.2 Definitions of Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the FAS.

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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by randomized treatment groups.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each randomized and end of the Titration Period treatment groups using descriptive statistics. Continuous demographic variables include age, height, weight, and BMI; categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (<18.5, 18.5 to <25, 25 to ≥30), race, and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using ISI, PGI-I, and Quality of Sleep Rating.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization WHO Drug Global March 2019 or later. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by randomized treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD PT.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be conducted on the FAS.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses are as follows:

- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.

- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of Titration Period dose groups.

Primary and Secondary endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.

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.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of AEs will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

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

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

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to a Customized MedDRA Query (CMQ) PT as cataplexy-related events, as well drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately. In addition, 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, as per the Adjudication Committee description.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and end of Titration Period dose using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

9.7.1.8.4 VITAL SIGNS

Mean changes from baseline in vital signs (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and out-of-range vital signs will be summarized by end of Titration Period dose groups for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

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 4). 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 (Safety Analysis Set), by end of Titration Period dose and time point.

Table 4 Clinically Notable Vital Sign Criteria

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

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at Screening and at the end of the Titration Period. The incidence of abnormal ECG findings will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL Use) and Cohort 2 (Frequent ZOL Use) using descriptive statistics. Shift tables will present changes from baseline in ECG interpretation (categorized as normal and abnormal) by time point.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

Urine drug test results and pregnancy test results will also be listed.

9.7.2 Determination of Sample Size

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for ZOL. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to determine whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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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 should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

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

- Recorded data from automated instruments such as Interactive Voice/Web Response System (IxRS), x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

- Electronic Patient-Reported Outcome by self-reported measures

11.4 Recording of Data

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

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

The efficacy assessments are evaluated based on the data entered into electronic Patient-Reported Outcome. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

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

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, 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 principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designated contractor, or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/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.

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;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				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, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	• Barbiturates • Benzodiazepines • gamma-aminobutyric acid (GABA) analogues • Hydantoins • Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter [OTC])	• Diphenhydramine HCl • Carbinoxamine • Doxylamine • Dimenhyrinate • Triprolidine • Bromopheniramine • Chlorphenamine • Hydroxazine
Antihistamines with known sedating effects	• Non-sedating, eg, Claritin™ is not prohibited
Anxiolytics with known sedating effects	• Lorazepam • Alprazolam • Buspirone

Category	Medication
Strong CYP3A inhibitors	• Amiodarone • Bocepravir • Clarithomycin • Cobicistat • Conivaptan • Danoprevir • Diltizem • Elteravir • Fluvoxamine • Grapefruit juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telapravir • Telethromycin • Tipranavir • Troleandomycin • Voriconazole
Moderate CYP3A inhibitors	• Amprenavir • Aprepitant • Atazanavir • Casopitant • Cimetidine • Ciprofloxacin • Clotrimazole • Crizotinib • Cyclosporin • Darunavir • Dronadarone • Erythromycin • Faldaprevir • Fluconazole • Fluvoxamine • Imatinib • Netupitant • Tofisopam • Verapamil

Category	Medication
Cytochrome P450 (CYP)3A inducers	• Avasimibe • Bosentan • Carbamazepine • Efavirenz • Enzaluteamide • Etravirine • Lersivirine • Modafinil • Mitotane • Nafcillin • Phenobarbital • Phenytoin • Rifabutin • Rifampin • St John's Wort • Troglitazone • Talviraline • Thioridazine
Hypnotics	• Melatonin • Prescribed or OTC
Herbal preparations with sedating effects	• -
Monoamine oxidase inhibitors (MAOIs)	• -
Opioid Analgesics	• -
Muscle relaxants (centrally-acting) with known sedating effects	• GABA analogues • Hydantoins • Phenyltriazines
Other	• Warfarin, heparin, ticlopidine • Systemic isoretinoin • Systemic glucocorticoids

Appendix 3 Extension Phase

Study Design and Plan

The Extension Phase comprises a Maintenance Period of up to 12 weeks in duration, and a Follow-up Period visit that is to occur 4 weeks after the end of the Maintenance Period.

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of Lemborexant (LEM) that they took at the end of the Titration Period. Subjects will subsequently return to clinic at the visit as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, and study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Maintenance Period).

End of Study

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

Study Drug Supplies

Subjects will enter the Extension Phase from the Titration Phase of the Core Study, taking the same dose of LEM that was their final dose of the Titration Phase, ie, LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Schedule of Procedures/Assessments

Table 5 presents the Schedule of Procedures and Assessments for the 12-week Extension Phase.

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 - Extension

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				
C-SSRS	X	X	X	X
Prior and concomitant medications	X	X	X	X
Study drug compliance	X		X	X
Dispense study drug				
Retrieve unused study drug	X		X	X
Physical examination[e]	X	X	X	X
Vital signs and weight	X	X	X	X
Clinical laboratory tests[f]	X		X	X
Urine drug screen[g]	X		X	X
Urine pregnancy test[h]	X		X	X
Serum pregnancy test[h,i]				X
12-Lead ECG[j]	X		X	X
Adverse events[k]	X	X	X	X

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 - Extension

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram.

All visits to be done within ±7 days of the schedule.

a: The Follow-up Visit will be conducted 4 weeks after the end of the Extension Phase.
b: Subjects who discontinue study drug prematurely at any time after entering the Extension will be encouraged to return to the site as soon as practicable (preferably within 7 days).
c: During Early Termination and unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.
d: Assessments during an Unscheduled Visit to be conducted at the discretion of the investigator.
e: A full physical examination will be conducted at Visit 4 and 5 and at the Early Termination and Unscheduled Visit at the discretion of the investigator.
f: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
g: Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
h: Female subjects of child-bearing potential only.
i: To be conducted if urine pregnancy testing is positive
j: The ECG should be repeated if a clinically significant abnormality (as determined by the investigator) is observed.
k: 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 9.5.1.5, Adjudication Committee

Statistical Analyses

All statistical analyses will be the responsibility of the Biostatistics Department of Eisai. Statistical programming and analyses will be performed using SAS or other validated software.

Safety Analyses

The primary focus of data summarization for the Extension Phase will be on safety and tolerability. Evaluations of safety data will be performed on the Safety Analysis Set.

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-312

Study Protocol Title: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia

Investigational Product Name: E2006\Lemborexant

IND Number: 111871

SIGNATURES

Authors:

PPD

Eisai, Inc

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Investigational Product Name:	E2006\Lemborexant
IND Number:	111871

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International 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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Investigational Product Name:	E2006/Lemborexant
Indication:	Insomnia
Phase:	3b
	V1.0 12 Apr 2019 (original protocol)
IND Number:	111871
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006

Name of Active Ingredient: Lemborexant

Study Protocol Title

A Multicenter, Pilot Study to Evaluate Next-Dose Transition From Zolpidem to Lemborexant for the Treatment of Insomnia

Investigator(s)

Unknown

Sites

Approximately 15 sites within the United States of America

Study Period and Phase of Development

Phase 3b pilot study

Estimated duration of up to 38 weeks from first subject in to last subject's last visit.

Objectives

Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking zolpidem tartrate immediate release (ZOL-IR) or zolpidem tartrate extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

Secondary Objectives

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking zolpidem (ZOL)

Exploratory Objective(s)

None

Study Design

E2006-A001-312 is a multicenter Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. The Pretreatment and Treatment Phases will comprise the Core Study. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted.

Core Study

Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

Screening Period

During the Screening Period, subjects will be required to bring the container of their prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the frequency of ZOL is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing these data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days out of the allowable 21-day Screening Period in order to be eligible for study inclusion.

Subjects will return to clinic at the end of the Screening Period. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Baseline Periody

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible will enter the Titration Period.

Treatment Phase

Titration Period

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep at night. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed. Subjects will be instructed to not alter (ie, break or cut) their tablets of LEM.

Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will determine the nights on which they take LEM, with the requirement that they take LEM at least once per week during the 14–day Titration Period.

Cohort 2 (Frequent Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.
For subjects with a starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site should they feel that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
For subjects with a starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site should they feel that LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.
At the time of LEM dose change during the Core Study, the reason for the dose change will be recorded in the case report form (CRF). Subjects will be allowed 1 LEM dose adjustment during the Titration Period. Every morning, subjects will enter their insomnia drug use data into the data collection system, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating. The ISI will be completed at each study visit except Follow-up Visit. .
Upon completion of the Titration Period, subjects will be eligible to enter the Extension Phase.

Extension Phase

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of LEM that they took at the end of the Titration Period. Subjects will subsequently return to clinic as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Treatment Phase for subjects not entering the Extension Phase or after the end of the Extension Phase, for subjects entering the Extension Phase).

End of Study

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

Number of Subjects

Approximately 110 subjects will be screened to provide approximately 60 subjects (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 in LEM5, 20 in LEM10]).

Inclusion Criteria

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) criteria for Insomnia Disorder, either currently or prior to ZOL use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 but fewer than 5 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

Exclusion Criteria

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

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

dosing).

3. Any history of moderate or severe obstructive sleep apnea (OSA)
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
13. 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 (A list of prohibited concomitant medications is presented in the protocol).
14. Used any pharmacologic modality of treatment for insomnia other than zolpidem, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
15. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
16. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
17. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)
18. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
19. Hypersensitivity to lemborexant or any of the excipients.
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
21. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
22. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years

23. History of drug or alcohol dependency or abuse within approximately the last 2 years
24. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent
25. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Core Study

Test drug:

LEM5 or LEM10 taken orally in tablet form at night within a few minutes of the time the subject intends to sleep, according to the subject's predetermined intermittent or frequent use schedule.

Comparator Drug: Not applicable

Extension Phase

Test drug:

LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Duration of Treatment

A maximum of 14 weeks:

2 weeks of LEM5 and/or LEM10 during the Treatment Phase of the Core Study,

12 weeks during the Extension Phase

Concomitant Drug/Therapy

Prohibited medications should not be used during the study. A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Phase.

Prohibited medications include moderate and strong cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers, and medications that have known sedating effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate CYP3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study. Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study.

Assessments

Screening Assessments (Core Study only)

Sleep Disorders Screening Battery (SDSB):

The SDSB will include:

- STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA
- IRLS: a subjective scale comprising 10 questions, which measures severity of symptoms of restless legs syndrome

Sleep Drug History Questionnaire

Subjects will be asked questions about their history and response to prior sleep medications.

Sleep Drug Experience Interview – Zolpidem

Subjects will be asked questions about their subjective experiences while taking ZOL at the end of the Screening Period.

Efficacy Assessments (Core Study only)

Patient Global Impression – Insomnia

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep. The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening.

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. The ISI will be completed at each study visit except Follow-up Visit.

Quality of Sleep Rating

The Quality of Sleep Rating is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

Sleep Drug Experience Interview – Lemborexant

Subjects will be asked questions about their subjective experiences while taking LEM at the end of the Titration Period.

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments (Core Study and Extension Phase)

Safety assessments will consist of monitoring and recording all adverse events (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. Subjects will be asked about falls at every visit.

Adjudication Committee

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

Columbia – Suicide Severity Rating Scale

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

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments.

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments. This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, PCP, opiates, benzodiazepines, barbiturates, and amphetamines.

Bioanalytical Methods

Not applicable.

Statistical Methods

The study endpoints for efficacy and safety will be presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed.

Primary Endpoint

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses, or preference to continue insomnia management with another health care provider).

Secondary Endpoints

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.

- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.

Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the Full Analysis Set.

Efficacy Analyses (Core Study only)

All efficacy analyses will be conducted on the FAS.

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.
- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.
- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall,
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of the Titration Period dose groups.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses (Core Study and Extension Phase)

Evaluations of safety data will be performed on the SAS.
The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical

laboratory variables, and vital signs will be summarized for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics using end of titration dose group. AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.
Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and PTs related to drug abuse liability, will be summarized seperately. The results of the deliberation of the Adjudication Committee will be reported separately.
In addition, 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, as per the Adjudication Committee description.

Other Analyses (Core Study)

Primary and secondary endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan.

Interim Analyses

No interim analyses are planned for this study.

Sample Size Rationale

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for zolpidem. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to evaluate whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BMI	Body mass index
BP	blood pressure
CBT-I	Cognitive Behavioral Therapy for Insomnia
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th ed
FAS	full analysis set
GABA	gamma-aminobutyric acid
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISI	Insomnia Severity Index
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
LEM	lemborexant
LEM5	Lemborexant 5 mg
LEM10	Lemborexant 10 mg
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
OSA	obstructive sleep apnea
PBO	placebo
PGI-I	Patient Global Impression of Insomnia
PT	preferred term
QTcF	Difference between QTc corrected by Fridericia's formulas
SAE	Serious adverse events
SAS	safety analysis set
SDSB	Sleep Disorders Screening Battery
SOC	system organ class
TEAE	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
ZOL	zolpidem
ZOL-ER	zolpidem tartrate extended release
ZOL-IR	zolpidem tartrate immediate release

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Title 21 of the United States Code of Federal Regulations [CFRs], Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate CRA[s], change of telephone number[s]). Documentation of IRB compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

Study progress is to be reported to IRBs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports, and inform the IRB of any reportable adverse events (AEs) per ICH guidelines and local IRB/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 within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB 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 (2013)
- ICH E6 Guideline for GCP (Committee for Proprietary Medicinal Products [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 US CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

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

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

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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 15 investigational sites in the United States of America.

The name, telephone and fax numbers of the Medical Monitor and other contact personnel at the contract research organization(s) (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Indication

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

7.1.1 Current Therapeutic Options

Treatments for insomnia include both non-pharmacological (Schutte-Rodin, et al., 2008; Morgenthaler, et al., 2006) and pharmacological treatments (Sateia, et al., 2017). Patients who undergo thorough diagnostic evaluations for insomnia symptoms are asked about their sleep and wake habits, since some cases of insomnia can be addressed by improving sleep hygiene. Principles of good sleep hygiene include regular bedtimes and waketimes, limiting alerting activities before bedtime, and limiting caffeine and alcohol intake, among others (Schutte-Rodin, et al., 2008). These techniques are often not adequate to address insomnia symptoms (Stepanski and Wyatt, 2003; Irish, et al., 2015).

Another commonly recommended non-pharmacological approach is the use of cognitive behavioral therapy for insomnia (CBT-I; Schutte-Rodin, et al., 2008). CBT-I includes techniques to minimize wakefulness at the time the patient intends to sleep. However, while there are data to support the effectiveness of CBT-I, sleep restriction is commonly a major component, and this may lead to daytime sleepiness, an unintended consequence of short sleep (Kyle, et al., 2014). In contrast, lemborexant's mechanism of action would avoid the daytime sleepiness caused by sleep restriction, while reducing wakefulness and facilitating sleep, which is an important underlying goal of CBT-I.

There are numerous drugs available for the treatment of insomnia, some available by prescription and many available over-the-counter. Many of the over-the-counter medicines lack empirical data from adequate, well-designed and controlled clinical trials to support their use (Rosen, et al., 2005); these include melatonin and antihistamines. Pharmacological treatments available by prescription and used clinically for insomnia include sedative hypnotics (benzodiazepines, nonbenzodiazepine gamma-aminobutyric acid (GABA)-releasing [GABAergics] agents), sedating antidepressants, melatonin agonists, and a DORA.

7.1.2 Lemborexant

Lemborexant belongs to the pharmacologic class of orexin receptor antagonists, a class of chemical compounds developed for the treatment for insomnia. To date, clinical proof of concept has been achieved by 6 orexin receptor antagonists (lemborexant, almorexant [ACT-078573], suvorexant [MK-4305], filorexant [MK-6096]), seltorexant [MIN-202], and nemorexant [ACT-541468]), demonstrating validity of the mechanism of action (Herring, et al., 2012; Hoever, et al., 2012; Connor, et al., 2016; Murphy, et al., 2017; De Boer, et al., 2018).

Nonclinical data show that lemborexant binds to and competitively antagonizes human orexin-1 receptor (OX1R) and orexin-1 receptor (OX2R) in vitro, with rapid association and dissociation kinetics at both receptors. In vitro data show that lemborexant does not substantially interact with other sleep-related receptors and channels (Beuckmann, et al, 2017). Lemborexant prevents [Ala^{11}, D-Leu^{15}]-orexin-B-induced plasma adrenocorticotropic hormone increase in rats, and promotes physiological sleep in mice and rats. In mice, lemborexant does not promote sleep when the orexin pathway has been functionally impaired. In rats, daily treatment for 3 consecutive weeks with lemborexant did not result in tolerance or wakefulness rebound upon treatment cessation, and did not elicit direct transitions from wakefulness to rapid eye movement (REM) sleep, a narcolepsy-like symptom. However, in strong emotional contexts, lemborexant induced cataplexy-like events in mice (Study W-20140712). Cataplexy has been noted in dogs dosed with another orexin antagonist, suvorexant, when presented with food enrichment (Belsomra, 2018), but the relationship to cataplexy symptoms in humans has not been established. At doses up to 300 mg/kg (300-fold higher than necessary for sleep promotion), lemborexant did not have any negative influence on motor coordination in mice, nor did it show any significant interaction with ethanol.

7.1.2.1 Clinical Experience With Lemborexant

The safety and efficacy of lemborexant for the treatment of insomnia disorder was confirmed in 2 pivotal Phase 3 studies, E2006-G000-303 (Study 303) and E2006-G000-304 (Study 304). In Study 304, lemborexant also demonstrated superior improvement on objective and subjective measures of sleep onset and maintenance compared to zolpidem tartrate extended release (ZOL-ER). Additional safety assessments pertinent to insomnia drugs, specifically regarding postural stability, were also conducted in study E2006-A001-108 and Study 304. In these studies, the safety of lemborexant on postural stability was superior compared to zolpidem (ZOL). Based on these data, a New Drug Application for lemborexant was submitted to the US Food and Drug Administration for the treatment of insomnia disorder in December 2018 and accepted for review in February 2019.

The safety and tolerability of lemborexant has been comprehensively evaluated in a broad patient population that includes subjects with insomnia disorder per Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) (with or without medical or psychiatric comorbidities), subjects with Alzheimer's disease and ISWRD, subjects with mild obstructive sleep apnea (OSA), and subjects with severe renal impairment or mild to

moderate hepatic impairment. Exposures included dosing of ≥12 months. Approximately 40% of subjects in the development program were elderly (≥65 years), providing extensive safety and tolerability profile for this important subpopulation at risk for insomnia.

Overall, of 2824 subjects with sleep disorders, 1848 received lemborexant, 714 received placebo (PBO), and 263 received ZOL.

No deaths were reported in subjects treated with lemborexant.

The overall incidence of treatment-emergent serious adverse events (SAEs) for subjects treated with lemborexant 5 mg (LEM5) and lemborexant 10 mg (LEM10) in the Phase 3 Pool was low (2.8% and 2.3%, respectively) but greater than for PBO (0.9%). However, when adjusted by duration of exposure, the overall incidence (subjects per patient-year) was similar to PBO (<0.1 for PBO, 0.1 for LEM5, and 0.1 for LEM10). The overall rate (events per patient-year) of treatment-emergent SAEs when adjusted by duration of exposure was <0.1 for PBO, <0.1 for LEM5, and <0.1 for LEM10.

There were no differences in the types of treatment-emergent SAEs reported during long-term treatment with lemborexant. There were no differences in treatment-emergent SAEs based on intrinsic factors, including age, sex, and body mass index (BMI) of subjects. Notably, the incidence of treatment-emergent SAEs in the elderly was consistent with that in younger subjects.

Across the Phase 3 studies of 303 and 304 (total subjects=1945), the majority of treatment-emergent SAEs occurred as singular events in 1 subject only. The SAEs of osteoarthritis (0% for PBO, 0.1% for LEM5, 0.4% for LEM10), rib fracture (0.2% for PBO, 0% for LEM5, 0.1% for LEM10), and diabetic neuropathy (0% for PBO, 0.3% for LEM5, 0% for LEM10) occurred in more than 1 subject across the PBO, LEM5, and LEM10 groups. One (0.1%) serious event of fall was reported in the LEM5 group.

7.1.2.2 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

None.

7.2 Study Rationale

Switching of medications for insomnia occurs often in clinical practice based on clinical response, AEs, reimbursement patterns, or physician and patient preference. However, there is no clinical trial experience or dosing guidance for transitioning from currently approved treatments for insomnia to lemborexant. Study E2006-A001-312 (Study 312) is designed as a pilot study to assess the dosing approach of directly transitioning from ZOL, the most commonly prescribed sleep aid (Bertisch, et al., 2014), to lemborexant, without tapering the ZOL dose, and with the opportunity for lemborexant dose titration. This study will provide initial information on patient satisfaction after switching to lemborexant, with secondary objectives assessing subjective quality of sleep and tolerability. If issues are identified

regarding patient satisfaction, tolerability, or quality of sleep, other dosing paradigms can be assessed in future studies to mitigate these issues.

7.2.1 Entry Criteria Rationale

Subjects with insomnia disorder per DSM-5 criteria (with or without medical or psychiatric comorbidities) will be eligible for study entry, which is representative of the typical target outpatient population. All subjects who are willing to substitute ZOL with LEM, regardless of the reason(s), will be eligible, and the reason(s) will be captured during screening. While it is anticipated that most eligible subjects would substitute ZOL with LEM due to dissatisfaction with ZOL, other reasons, as determined by input from Key Opinion Leaders (KOLs) in Sleep Medicine, may include, but are not limited to, concerns regarding ZOL side effects, eg, parasomnias. Including subjects with these various reasons is representative of the real-world outpatient setting.

While the approved dosing instructions for women and patients ≥65 stipulate that the lower dose of ZOL is to be prescribed, many women and elderly patients may be taking the higher dose. Therefore, for generalizability of the results of the study to the patient population, any stable dosing regimen will be eligible, including those subjects taking higher than approved doses up to the maximum approved (10 mg IR or 12.5 mg ER).

7.2.2 Rationale for Titration Schedule and Duration

Since this study is designed to reflect common clinical practice, flexibility to titrate the dose up or down is built into the dosing regimen. In the outpatient setting, clinicians typically advise patients to allow themselves one week to adjust to a new medication; therefore, subjects assigned to LEM5 will be encouraged to remain on their dose of LEM for 1-week prior to titrating up to LEM10, and those assigned to LEM10 will be encouraged to remain on their dose of LEM prior to titrating down to LEM5 after one week.

Subjects who intermittently use ZOL are expected to be more likely to be started on LEM5 in the outpatient setting, as they are not chronically exposed to, or reliant upon, pharmacologic insomnia treatments. Therefore, all subjects in Cohort 1 will be started on LEM5 during the Titration Period of the Treatment Phase.

The duration of the Treatment Phase of the Core Study is set at 2 weeks, since that amount of time is deemed reasonable by expert opinion from consultation with KOLs in Sleep Medicine for subjects to decide if they wish to continue on lemborexant.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate the proportion of adult (≥18 years) subjects with insomnia disorder taking ZOL immediate release (ZOL-IR) or extended release (ZOL-ER), intermittently or frequently, who transition to lemborexant 5 mg (LEM5) or 10 mg (LEM10), after 2 weeks of receiving lemborexant (LEM).

8.2 Secondary Objectives

- To evaluate the proportion of subjects who increase from LEM5 to LEM10 or decrease from LEM10 to LEM5 during the 2-week Titration Period
- To evaluate the subject impression of treatment using the Patient Global Impression of Insomnia (PGI-I) at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Insomnia Severity Index (ISI) compared with Baseline at the end of the 2-week Titration Period
- To evaluate LEM5 and/or LEM10 scores on the Quality of Sleep Rating scale compared with Baseline at the end of the 2-week Titration Period
- To evaluate the safety and tolerability of LEM in subjects previously taking ZOL

8.3 Exploratory Objective(s)

None

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, Phase 3b pilot study evaluating the transition of LEM when administered as a replacement for ZOL-IR or ZOL-ER. Adult (≥18 years) subjects are eligible for participation if they have been diagnosed with insomnia disorder per the DSM-5th Ed (American Psychiatric Association, 2014), are currently receiving ZOL as monotherapy for insomnia, and who agree to substitute zolpidem tartrate immediate release (ZOL-IR) or ZOL-ER with LEM, regardless of the reason.

The study will consist of 3 phases: a Pretreatment Phase (consisting of up to a 3-week Screening Period and a 1-day Baseline Period), a Treatment Phase (consisting of a 2-week Titration Period), and an Extension Phase consisting of the Maintenance Period up to 12 weeks and the Follow-up Period 4 weeks in duration immediately following the end of the Treatment Phase. A Follow-up Period visit occurring 4 weeks after the end of the Extension Phase (or Treatment Phase, for subjects not entering the Extension Phase) will be conducted. The Pretreatment and Treatment Phases will comprise the Core Study. The Extension Phase is described in detail in Appendix 3.

During the Screening Period, eligible subjects will prospectively record the number of days ZOL is taken over 21 days using a Data Collection System. Based on these data, subjects will be assigned to 1 of 2 cohorts of ZOL use frequency:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). Within Cohort 2, subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

Subjects who remain eligible for the study will enter the Baseline Period.

Approximately 110 subjects will be screened to provide approximately 60 subjects for randomization (20 subjects in Cohort 1 and 40 subjects in Cohort 2 [20 subjects in LEM5 and 20 subjects in LEM10]).

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

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

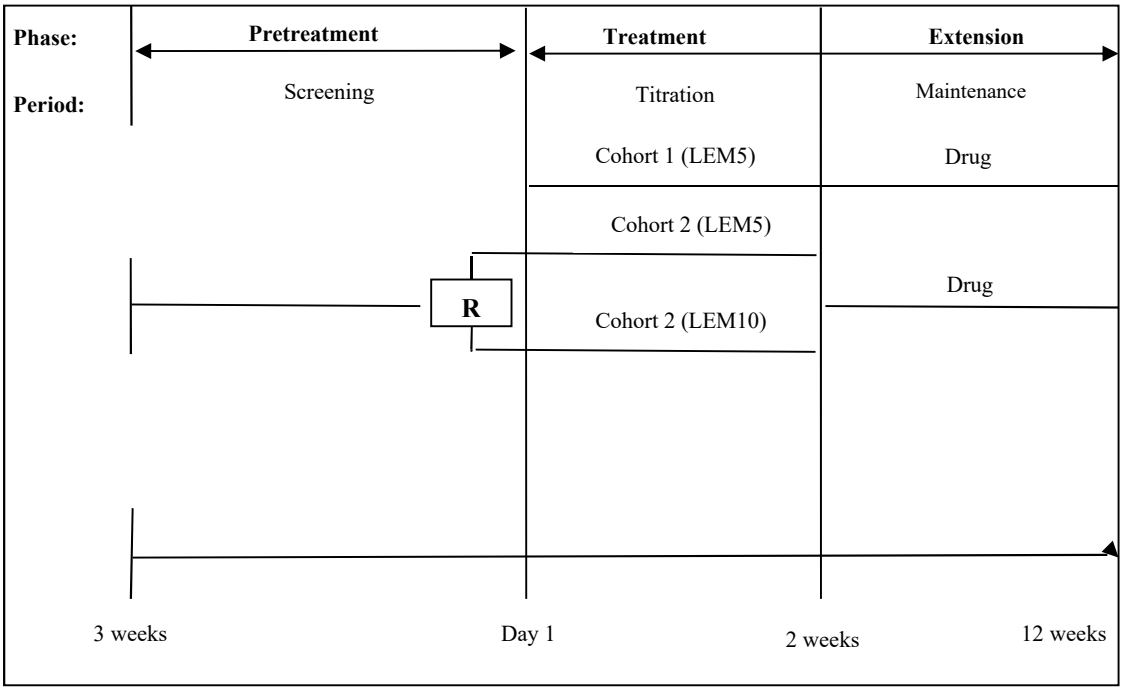

Figure 1 Study E2006-A001-312 – Study Design

LEM5 = lemborexant 5 mg, LEM5 = lemborexant 5 mg, R = Randomization

9.1.1 Pretreatment Phase (Core Study)

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks) and 1-day Baseline Period, during which subjects will be assessed for eligibility to participate in the study.

9.1.1.1 Screening Period (Core Study)

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. 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. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of insomnia per the DSM-5 (American Psychiatric Association, 2014), be currently receiving ZOL as monotherapy for insomnia, and agree to substitute zolpidem tartrate immediate release (ZOL-IR) or extended release (ZOL-ER) with LEM, regardless of the reason.

During the Screening Period, subjects will be required to bring the container of their currently prescribed ZOL to the site for verification of prescribed medication and dose. Subjects will be provided with, and trained in the use of, a data collection system to record the dose and frequency of ZOL which is taken during the 3-week Screening Period. Site staff will instruct subjects to complete data entry every morning and will emphasize the importance of providing this data. During the Screening Period, subjects will continue to take ZOL at the dosage strength prescribed by their health-care provider (ZOL-IR 5 mg or 10 mg or ZOL-ER 6.25 mg or 12.5 mg). Subjects must enter data into the data collection system for at least 14 (preferably contiguous) days of the 21-day Screening Period in order to be eligible for study inclusion.

Subjects will return to clinic at the end of the Screening Period. For subjects who remain eligible for study enrollment, the second Screening Period visit will serve as that subject's Baseline Period, and will occur on the same day. Based on ZOL use during the Screening Period (which must match the treatment history ascertained at the beginning of the Screening Period), subjects will be assigned to 1 of 2 cohorts as follows:

- Cohort 1 (Intermittent ZOL Use): Subjects who took ZOL at least 3 or 4 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): Subjects who took ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will begin the Titration Period on lemborexant 5 mg (LEM5). For Cohort 2, (n=40), subjects will be randomized to 1 of 2 Treatment Groups (LEM5 or LEM10) in a 1:1 ratio.

9.1.1.2 Baseline Period (Core Study)

The Baseline Period (1-day) begins when eligible subjects have been assigned to a treatment cohort. Subjects who are not eligible will conclude their participation and will be considered screen failures. Upon completion of the Baseline Period, subjects who remain eligible by meeting the criteria for inclusion/exclusion (Sections 9.3.1 and Section 9.3.2) will enter the Titration Period.

9.1.2 Treatment Phase (Core Study)

The Treatment Phase will consist of a 2-week Titration Period and 1-day Follow-up Visit to occur 4 weeks after completion of the Titration Period (or as soon as possible following early discontinuation) for subjects not entering the Extension Phase. Subjects who meet all of the inclusion criteria and none of the exclusion criteria at the Baseline Visit, and who have entered ZOL medication use data into the Data Collection System for at least 14 of the 21-day Screening Period as specified in the Inclusion Criteria, are eligible to enter the Treatment Phase of the study.

9.1.2.1 Titration Period (Core Study)

During the 2-week Titration Period, subjects will be provided with a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time that they intend to sleep. Study restrictions pertaining to duration of time spent in bed, use of alcohol, and timing of meals will be discussed with the subject at each visit during the Treatment and Extension Phases. Subjects will be instructed to not alter (ie break or cut) their tablets of LEM.

Subjects assigned to Cohorts 1 and 2 will self-administer the study medication according to the following regimens:

- Cohort 1 (Intermittent ZOL Use): Subjects in this cohort will determine the nights on which they take LEM, with the requirement that they take LEM at least once per week during the 2-week Titration Period.
- Cohort 2 (Frequent ZOL Use, Treatment Groups A and B): Subjects in these cohorts will take LEM at least 5 nights per week during the 2-week Titration Period.

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For subjects starting dose of LEM5 in Cohorts 1 and 2, subjects will be encouraged (but not mandated) to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For subjects starting dose of LEM10 in Cohort 2, subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10

should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the case report form (CRF).

Every morning, subjects will enter their insomnia drug use data into the data collection system, and, provided an insomnia drug was taken the night prior, PGI-I and Quality of Sleep Rating will be completed. The ISI will be completed at each clinic visit except Follow-up Visit.

Upon completion of the Titration Period, subjects may be eligible to enter the Extension Phase (Appendix 3).

9.1.2.2 Follow-Up Period

For subjects not entering the Extension Phase, the Follow-up Period will start immediately after the end of the Treatment Phase and last for 4 weeks. The purpose of the Follow-up Period is to assess adverse events and other safety parameters. Subjects will be instructed to continue insomnia management with the health-care provider who had been treating them prior to study entry, if they so desire.

9.1.3 Extension Phase

Subjects who complete the Core Study and wish to continue taking LEM will enter the 12-week Extension Phase. Subjects will continue the LEM dose and regimen established during the Titration Period; however, the dose may be titrated up or down depending on response and tolerability, per subject input and investigator judgement. For subjects who are eligible for the Extension Phase but who do not wish to continue study participation, the reason for discontinuation from the study will be recorded. At the end of the Extension Phase, the Follow-up Period will begin, and last for 4 weeks.

Details of the Extension Phase are provided in Appendix 3.

9.2 Discussion of Study Design, Including Choice of Control Groups

See Section 7.2, Study Rationale.

9.3 Selection of Study Population

Approximately 60 subjects will be enrolled at approximately 15 sites in the United States of America. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Male or female, 18 years or older, at the time of informed consent
2. Meets the DSM-5 criteria for Insomnia Disorder, either currently or prior to zolpidem use, as follows:
   - Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. Reports spending at least 7 hours in bed per night
4. History of intermittent (taking ZOL at least 3 or 4 nights per week), or frequent use (at least 5 nights per week) of ZOL-IR or -ER, for at least 1 month
5. Confirmation of intermittent or frequent use of ZOL (based on review of drug use data). Intermittent use is defined as taking ZOL at least 3 but fewer than 5 nights per week, for at least 2 weeks each of the 3-week Screening Period. Frequent use is defined as taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period
6. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
7. Willing not to start another pharmacologic treatment for the management of insomnia during the subject's participation in the study

9.3.2 Exclusion Criteria

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

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

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

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

3. Any history of moderate or severe OSA
4. Current evidence of a clinically significant, active respiratory disorder other than mild OSA. This includes bronchiectasis, emphysema, asthma, chronic obstructive pulmonary disease or any other pulmonary disorder identified by review of medical history or physical examination, and which in the opinion of the investigator, could compromise the subject's safety or interfere with study assessments
5. A current diagnosis of periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
   - STOP-Bang score ≥5 (subjects previously diagnosed with mild OSA are not excluded)
   - International Restless Legs Scale (IRLS) score ≥16
6. Habitually naps during the day more than 3 times per week
7. 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
8. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone calls or preparing and eating food while sleeping), whether spontaneous or associated with a pharmacological sleep agent.
9. Takes a dose of ZOL-IR >10 mg per night, or ZOL-ER>12.5 mg per night
10. Takes a dose of ZOL that is lower than what is prescribed
11. Reports having altered ZOL tablets
12. Unwilling to forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study
13. 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 (A list of prohibited concomitant medications is presented in the protocol).
14. Used any pharmacologic modality of treatment for insomnia other than ZOL, including marijuana, within 1-week or 5 half-lives, whichever is longer, before the Screening Period
15. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG
16. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS])
17. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS)

18. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, and renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded.
19. Hypersensitivity to lemborexant or any of the excipients.
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study.
21. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery, which requires only local anesthesia and which can be undertaken as a day case without inpatient stay postoperatively, need not result in exclusion if in the opinion of the investigator this operation does not interfere with the study procedures and patient safety.
22. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
23. History of drug or alcohol dependency or abuse within approximately the last 2 years
24. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent.
25. 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.

9.4 Treatments

9.4.1 Treatment(s) Administered

The following treatments will be administered to subjects in the Core Study (Table 1).

Table 1 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
Lemborexant	5 mg	Tablet	1×5 mg tablets, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days
Lemborexant	10 mg	Tablet	1×10 mg tablet, once at night within a few minutes of the time the subject intends to sleep, according to the predetermined intermittent or frequent use schedule	14 days

Subjects will be allowed 1 LEM dose adjustment during the Titration Period, according to the following guidelines:

- For Cohorts 1 and 2A (starting dose of LEM5), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that LEM5 is not fully effective for treatment of their insomnia. Subjects who call the site will then be instructed by phone to take LEM10 within a few minutes of the time they intend to sleep.
- For Cohort 2B (starting dose of LEM10), subjects will be encouraged to remain on their assigned dose for 7 days before calling the site to report that the dose of LEM10 should be reduced. Subjects will then be instructed to take LEM5 within a few minutes of the time they intend to go to sleep.

At the time of any LEM dose change during the Titration Period, the reason for the dose change will be recorded in the CRF.

9.4.2 Identity of Investigational Product

Lemborexant will be supplied by the sponsor in labeled containers.

Study drug must be stored as instructed on the study drug label. Study drug must be kept in a secure location and carefully stored at the study site within its original container. The sponsor will provide the study drug packaged as open-label supplies. Each subject's study drug will consist of lemborexant tablets supplied in bottles.

9.4.2.1 Chemical Name, Structural Formula of Lemborexant

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

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Based on ZOL use during the Screening Period, subjects will be assigned to 1 of 2 cohorts as shown below:

- Cohort 1 (Intermittent ZOL Use): taking ZOL at least 3 but fewer than 5 nights per week, for each of at least 2 weeks of the 3-week Screening Period, or
- Cohort 2 (Frequent ZOL Use): taking ZOL at least 5 nights per week, during, at minimum, the last 2 weeks of the 3-week Screening Period

All subjects (n=20) in Cohort 1 will receive LEM5. Subjects in Cohort 2 will be randomized to 1 of 2 Treatment Groups: Cohort 2A (20 subjects) will start on LEM5, and Cohort 2B (20 subjects) will start on LEM10.

9.4.4 Selection of Doses in the Study

The doses to be administered are LEM5 and LEM10. In December 2018, these doses were submitted for approval in the US for the indication of insomnia. These doses were originally selected after conducting a dose-finding study (E2006-G000-201) after which their safety and efficacy were confirmed in 2 Phase 3 studies, Studies 303 and 304.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be provided a supply of LEM5 and LEM10 to be taken at home within a few minutes of the time they intend to sleep. Subjects will be instructed on study restrictions

pertaining to duration of time spent in bed, use of alcohol, and timing of meals. Subjects will be instructed not to alter (ie, break or cut) their tablets of LEM.

9.4.6 Blinding

This is an open-label study with randomization to treatment for subjects assigned to Cohort 2.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent or 30 days before first dose/administration of study drug, if appropriate) will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

A subject must not have used any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

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

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that strong and moderate cytochrome P450 (CYP)3A inhibitors and all CYP3A inducers will not be permitted at any time for any duration during the study.

9.4.7.1 Drug-Drug Interactions

Coadministration with moderate and strong CYP3A inhibitors may moderately increase exposure to lemborexant, and CYP3A inducers may markedly decrease lemborexant exposure. Drug interactions with lemborexant are described in further detail in the Investigator's Brochure; prohibited concomitant medications are described in Section 9.4.7.2 and listed in Appendix 2.

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.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (Appendix 2) should not be used during the study. A subject must discontinue any prohibited prescription or over-the-counter medications within 1-week or 5 half-lives, whichever is longer, before the Treatment Period.

Prohibited medications include strong and moderate CYP3A inhibitors and all CYP3A inducers. Prohibited therapies also include: any pharmacologic treatment for insomnia disorder (with the exception of ZOL use during the Screening Period only); medications that are used for the purpose of inducing sleep (hypnotics) and medications that have known sedating effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants).

If a medication is not on the list of prohibited medications (Appendix 2) 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 2, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. Note that strong and moderate CYP3A inhibitors and all CYP3A4 inducers will not be permitted at any time for any duration during the study.

If a subject starts any prohibited medication or a new treatment/modality for insomnia disorder, he/she must discontinue from the study.

Subjects must forgo alcohol consumption within 3 hours of bedtime for the duration of participation in the study. If subjects cannot comply after counseling, they may be discharged from the study.

9.4.8 Treatment Compliance

Compliance will be assessed by examination of bottles returned to the investigator at the end of the Titration Period.

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 for the institution where the study is to be conducted

- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor. 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 [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance.

Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned

to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity.

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical, sleep, and psychiatric history will be recorded as designated in the Schedule of Procedures/Assessments (Table 3). All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations will be performed, as designated in the Schedule of Procedures/Assessments (Table 3). A full physical examination will be performed, excluding a urogenital examination unless there are special circumstances and at the discretion of the investigator. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.2.2 Sleep Drug History Questionnaire

At Screening, subjects will complete a questionnaire reporting their history and response to prior sleep medications, as well as their motivation for participating in the study.

9.5.1.2.3 Sleep Disorder Screening Battery

A lifetime history of sleep disorders will be obtained only at the 1st Screening Visit. For insomnia complaints, this history will include clinical, qualitative assessment and/or confirmation that subjects meet diagnostic criteria for insomnia disorder. The history will also include information regarding habitual sleep timing, bedtime routines, and other aspects

of sleep hygiene to determine eligibility and to exclude subjects whose insomnia symptoms appear to be due to poor sleep hygiene or to frequent napping, for example.

For the detection of other sleep disorders, the Sleep Disorders Screening Battery (SDSB) will be administered (see below).

The SDSB will include the following, to be self-administered by subjects:

- The STOP Bang: a list of 8 questions to be answered Yes or No, which screens subjects for OSA (Chung et al., 2008)
- The IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome (Abetz et al., 2006).

9.5.1.2.4 SLEEP DRUG EXPERIENCE INTERVIEW – ZOLPIDEM

At the end of the Screening Period, subjects will be asked questions about their subjective experiences while taking ZOL. The responses will be compared to the Sleep Drug Experience Interview – Lemborexant, which is done at the end of the Treatment Phase, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 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. The ISI will be completed at each study visit except Follow-up Visit.

9.5.1.3.2 PATIENT'S GLOBAL IMPRESSION – INSOMNIA

The PGI-I is a self-report assessment of subject perception of the effects of a medication on their sleep (Herring, et al., 2018). The PGI-I 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). The PGI-I will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.3 QUALITY OF SLEEP RATING

The Quality of Sleep Rating (Krystal and Edinger, 2008) is a self-reported scale in which subjects are asked, "How would you rate the quality of your sleep last night, with 1 being extremely poor, 5 being not good or poor, and 9 being extremely good?" For Quality of Sleep, higher values are better. The Quality of Sleep Rating will be completed each morning following a dose of ZOL or LEM taken the prior evening during the Screening, Baseline, and Titration Periods.

9.5.1.3.4 SLEEP DRUG EXPERIENCE INTERVIEW – LEMBOREXANT

At the end of the Titration Period, subjects will be asked questions about their subjective experiences while taking LEM. The responses will be compared to the Sleep Drug Experience Interview – ZOL, which is done at the end of the Screening Period, in order to provide qualitative information regarding an individual's subjective experience with LEM compared to ZOL.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity), regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations. Subjects will be asked about falls at every visit.

Sponsor's grading for laboratory values are presented in Appendix 1.

Adjudication Committee

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms (PTs) 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 [standard MedDRA query (SMQ) narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [faintness], and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff will be instructed to query subjects who report any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events considered serious.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lemborexant (in doses of 5 mg and 10 mg).

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, x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase and for 7 days or 5× the half-life after the last dose, whichever is longer. SAEs will be collected for 28 days after the last dose or for 5× the half-life, whichever is longer.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.8 for a description of the C-SSRS).

The number (percentage) of subjects with treatment emergent adverse events (TEAEs) of cataplexy or other events that are characterized according to the customized MedDRA query PT as cataplexy related events will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately.

Customized MedDRA Queries for AEs that could potentially be considered cataplexy will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. All AEs must be followed for 28 days, or 5× the half-life, whichever is longer after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

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

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

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

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

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

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

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

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed 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.

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, including, cataplexy, potential cataplexy, convulsion, fall, and seizure, should always be considered adverse events and reported on the Adverse Event CRF and on the event-specific CRFs designed to collect additional information on specific events.

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

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	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Clinical laboratory tests during the Screening, Baseline, and Titration Periods will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

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

9.5.1.5.5 Vital Signs, Height, and Weight Measurements

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

9.5.1.5.6 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 3). Documentation of the physical examination 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 Adverse Events CRF.

9.5.1.5.7 Electrocardiograms

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

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

9.5.1.5.8 Other Safety Assessments

Columbia-Suicide Severity Rating Scale

The C-SSRS assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Suicidality will be assessed as designated in the Schedule of Procedures and Assessments (Table 3), using a site-administered version of the C-SSRS (Posner, et al., 2011).

Pregnancy Test

A urine pregnancy test or serum pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months as designated in the Schedule of Procedures/Assessments (Table 3).

Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 3). This sample will be tested for common drugs of use/abuse: eg, propoxyphene, cocaine metabolites, cannabinoids, methadone, phencyclidine (PCP), opiates, benzodiazepines, barbiturates, and amphetamines.

9.5.2 Schedule of Procedures/Assessments – Core Study

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Core Study.

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		ET[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0[g]	2	6		
Procedures/Assessments							
Demography	X						
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Sleep Drug History Questionnaire	X						
Sleep Disorder Screening Battery[g]	X						
Insomnia Severity Index	X	X	X	X		X	X
C-SSRS	X	X[h]	X	X	X	X	X
Medical, sleep, psychiatric history	X						
Prior and concomitant medications	X	X	X	X	X	X	X
Dispense study drug			X	X			
Retrieve unused study drug				X		X	
Study drug compliance				X		X	X
Physical examination[i]	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X
Height	X						

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		ET[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0[g]	2	6		
Procedures/Assessments							
Clinical laboratory tests[j]	X		X	X		X	X
Urine drug screen[k]	X	X	X	X		X	X
Urine pregnancy test[l]	X	X	X	X		X	X
Serum pregnancy test[l,m]	X						X
12-lead ECG[n]	X	X	X	X		X	X
PGI-I[o]	X	X[h]	X	X		X	X
Quality of Sleep Rating[o]	X	X[h]	X	X		X	X
Sleep Drug Experience Interview - zolpidem		X				X	X
Sleep Drug Experience Interview - lemborexant				X			
Adverse events[p]	X	X	X	X	X	X	X

Table 3 Schedule of Procedures and Assessments in E2006-A001-312 – Core Study

Phase	Pretreatment			Treatment			
Period	Screening		Baseline	Titration	Follow-Up[a]		
Visit	1	2a[b]	2b[b]	3[c]		E T[d,e]	UNS[e,f]
Week	-3 (Days -21 to -1)	-	0[g]	2	6		
Procedures/Assessments							

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram, PGI-I = Patient Global Impression – Insomnia, T = Termination Visit, UNS = Unscheduled Visits
All visits to be done within ±7 days of the schedule, except for Visits 2, 3 and 4, which must be done within ±3 days.

a: The Follow-up Visit will be conducted 4 weeks after the End of Study Visit for subjects who completed the Titration Period but do not enter the Extension Phase.
b: Subjects will return to clinic at the end of the Screening Period. The Baseline Period will occur on the same day for subjects who remain eligible for study enrollment. Assessments conducted at the end of the Screening Period (V2a) will serve as the assessments for the Baseline Period (V2b) if a subject is enrolled into the Treatment Phase. Assessments to be conducted at Baseline (but which are not done at V2a) will include clinical laboratory tests and dispensing of study drug.
c: This visit will represent the End of Study Visit for subjects who completed the Titration Period but are not entering the Extension Phase. Subjects should otherwise enter the Extension Phase immediately after completion of the Titration Period of the Core Study, in which case this visit will also serve as the first visit of the Extension Phase.
d: Subjects who discontinue study drug prematurely at any time after entering the Treatment Phase will be encouraged to return to the site as soon as practicable (preferably within 7 days) to complete the Early Termination Visit.
e: ECG will only be done during Early Termination and Unscheduled Visits if the results from the previous visit were deemed to be clinically significant by the investigator.
f: Assessments during Unscheduled Visits will be conducted at the discretion of the investigator.
g: Sleep Disorders Screening Battery comprises: STOP Bang and International Restless Legs Scale.
h: Data for Visit 2a will represent the Baseline Period (V2b) assessment if the subject is enrolled.
i: A full physical examination will be conducted at Visit 1. A brief physical examination will be conducted at Visit 2a, Visit 2b, Visit 3, and at the Follow-up Visit. For Early Termination and Unscheduled Visits, a physical examination will be conducted at the discretion of the investigator.
j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
k: Urine drug test at Unscheduled Visits will be conducted at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
l: Female subjects of child-bearing potential only.
m: To be conducted at Visit 1, and if urine pregnancy testing is positive.
n: The ECG should be repeated if a clinically significant (as determined by the investigator) abnormality is observed.
o: From the beginning of the Pretreatment Phase to the end of the Treatment Phase, and provided an insomnia drug was taken the night prior, PGI-I and Sleep Quality Rating data will be entered into the electronic data capture system by the subject.
p: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per Section 9.5.1.5, Adjudication Committee.

Table 5 presents the Schedule of Procedures/Assessments for the Extension Phase of the study.

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

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

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of nighttime sleep and daytime impairment complaints, the ISI will be evaluated for changes from baseline.

The PGI-I has been used in studies evaluating the impact of treatment for insomnia on the patients' global perceptions of sleep quality and quality of life.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. The C-SSRS, a standardized assessment required by regulatory authorities, will be used to evaluate any effects of lemborexant on suicidality.

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 in the Treatment Phase, 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 of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the CRO to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

A congenital anomaly, death during perinatal period, 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

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events—cataplexy, potential cataplexy, convulsion, fall, seizure—should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

Not applicable.

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 (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

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

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic response, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event CRF.

Sites will be assessed for the appropriateness of study drug storage and retrieval at the time of site selection. Required policies and procedures will be clearly communicated to the site to assess the site's capabilities and adherence to storage, dispensing, reconciliation, and retention of study drug.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and a snapshot of the database is obtained and released) and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. The study endpoints for efficacy and safety will presented by treatment group (LEM5 and LEM10) and by pooling across treatments within each cohort and overall. Missing data will not be imputed. Further details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

This study is designed to reflect clinical practice, in which patient satisfaction of the treatment after switching is an important consideration for maintaining a patient on that treatment. This was the basis for defining the outcome of transition to lemborexant. While sleep quality assessments are included as secondary outcomes in this pilot study to supplement the Phase 3 clinical trial data, it is not necessary to establish the absolute amount of improvement in sleep parameters, but rather whether the subject is satisfied enough to continue treatment with lemborexant.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of overall subjects who transition to LEM at the end of the Titration Period.

Transition to LEM is defined as a subject who remains on LEM at the end of the 2-week Titration Period and either 1) enters the Extension Phase, or 2) chooses to not enter the Extension Phase for reasons not related to LEM (including, but not limited to, time commitment related to the study, study-related travel expenses or preference to continue insomnia management with another health care provider).

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

- The proportion of subjects who transition to LEM at the end of the 2-week Titration Period within each Cohort.
- The proportion of subjects with positive medication effect rating on each PGI-I item at the end of the 2-week Titration Period by Cohort and overall using end of the Titration Period treatment.
- The change from Baseline in mean ISI score at the end of the Titration Period by Cohort and overall using end of the Titration Period treatment.
- The proportion of subjects in the LEM5 treatment groups with dose increasing to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 treatment group with dose decreasing to LEM5 at the end of the Titration Period in Cohort 2.
- The change from baseline in mean Quality of Sleep Rating at the end of the Titration Period by cohort and overall using end of the Titration Period treatment.

9.7.1.2 Definitions of Analysis Sets

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

Full Analysis Set (FAS) – All subjects who received at least 1 dose of LEM will be included in the FAS.

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 and treatment discontinuation. Other reasons for study treatment and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by randomized treatment groups.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each randomized and end of the Titration Period treatment groups using descriptive statistics. Continuous demographic variables include age, height, weight, and BMI; categorical variables include sex, age group (<65 years old; ≥65 years old), BMI group (<18.5, 18.5 to <25, 25 to ≥30), race, and ethnicity.

Characteristics of insomnia at Study Baseline will be summarized using ISI, PGI-I, and Quality of Sleep Rating.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization WHO Drug Global March 2019 or later. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by randomized treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD PT.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be conducted on the FAS.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

- The proportion of overall subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses are as follows:

- The proportion of subjects who transition to LEM after 2 weeks of treatment in the Titration Period will be displayed within each cohort.

- Proportion of subjects in each of the 4 items of the PGI-I will be summarized separately within each scale over time by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects whose response on the first 3 items of the PGI-I (medication effect) was neutral or negative at Baseline, but who recorded a positive effect on these items at the end of the Titration Period, and the proportion of subjects who rated the drug as being too strong or too weak at Baseline, but whose rating was "just right" at the end of the Titration Period (as data allow) will be reported.
- Change from Baseline of the total score from items 1 to 7 as well as items 4 to 7 on the ISI will be summarized at the end of the Titration Period by Cohort and overall using end of the Titration Period dose groups.
- The proportion of subjects in LEM5 who increased the dose to LEM10 at the end of the Titration Period by Cohort and overall.
- The proportion of subjects in LEM10 who decreased the dose to LEM5 at the end of the Titration Period will be displayed in Cohort 2. A graphical representation of changes between the 5 and 10 mg dose groups in each of the cohorts may also be presented.
- The change from baseline in mean Quality of Sleep Rating score for subjects at the end of the Titration Period will be summarized by cohort and overall using end of Titration Period dose groups.

Primary and Secondary endpoints may be analyzed by modeling methods if warranted. Details of all of the analyses will be specified in the Statistical Analysis Plan.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

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

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

AEs summaries, and abnormal findings will also be displayed based on the dose that the subjects were taking at the time of the findings.

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.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of AEs will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

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

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

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to a Customized MedDRA Query (CMQ) PT as cataplexy-related events, as well drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately. In addition, 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, as per the Adjudication Committee description.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and end of Titration Period dose using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

9.7.1.8.4 VITAL SIGNS

Mean changes from baseline in vital signs (ie, systolic and diastolic BP, pulse, respiratory rate, body temperature, weight) and out-of-range vital signs will be summarized by end of Titration Period dose groups for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

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 4). 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 (Safety Analysis Set), by end of Titration Period dose and time point.

Table 4 Clinically Notable Vital Sign Criteria

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

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at Screening and at the end of the Titration Period. The incidence of abnormal ECG findings will be summarized by end of Titration Period dose for Cohort 1 (Intermittent ZOL Use) and Cohort 2 (Frequent ZOL Use) using descriptive statistics. Shift tables will present changes from baseline in ECG interpretation (categorized as normal and abnormal) by time point.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

Urine drug test results and pregnancy test results will also be listed.

9.7.2 Determination of Sample Size

As a pilot study, sample size estimates are not based on statistical calculations.

This study will enroll 60 subjects across 3 treatment arms (Cohort 1, Cohort 2A, and Cohort 2B) to evaluate the proportion of subjects who transition to LEM as a substitute for ZOL. Twenty subjects will be assigned to Cohort 1 (Intermittent ZOL Use), and 40 subjects will be assigned to Cohort 2 (Frequent ZOL Use), with approximately 20 subjects randomized to receive LEM5 or LEM10 within Cohort 2. This sample size is deemed sufficient to inform whether the proposed strategies are sufficient to determine whether alternative strategies would be required to help understand how best to recommend safe and effective methods for transitioning from ZOL to LEM.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

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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 should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

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

- Recorded data from automated instruments such as Interactive Voice/Web Response System (IxRS), x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

- Electronic Patient-Reported Outcome by self-reported measures

11.4 Recording of Data

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

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

The efficacy assessments are evaluated based on the data entered into electronic Patient-Reported Outcome. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

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

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, 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 principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or designated contractor, or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/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.

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;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				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, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	• Barbiturates • Benzodiazepines • gamma-aminobutyric acid (GABA) analogues • Hydantoins • Phenyltriazines
Antihistamines (centrally-acting H1, including over-the-counter [OTC])	• Diphenhydramine HCl • Carbinoxamine • Doxylamine • Dimenhyrinate • Triprolidine • Bromopheniramine • Chlorphenamine • Hydroxazine
Antihistamines with known sedating effects	• Non-sedating, eg, Claritin™ is not prohibited
Anxiolytics with known sedating effects	• Lorazepam • Alprazolam • Buspirone

Category	Medication
Strong CYP3A inhibitors	• Amiodarone • Bocepravir • Clarithomycin • Cobicistat • Conivaptan • Danoprevir • Diltizem • Elteravir • Fluvoxamine • Grapefruit juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telapravir • Telethromycin • Tipranavir • Troleandomycin • Voriconazole
Moderate CYP3A inhibitors	• Amprenavir • Aprepitant • Atazanavir • Casopitant • Cimetidine • Ciprofloxacin • Clotrimazole • Crizotinib • Cyclosporin • Darunavir • Dronadarone • Erythromycin • Faldaprevir • Fluconazole • Fluvoxamine • Imatinib • Netupitant • Tofisopam • Verapamil

Category	Medication
Cytochrome P450 (CYP)3A inducers	• Avasimibe • Bosentan • Carbamazepine • Efavirenz • Enzaluteamide • Etravirine • Lersivirine • Modafinil • Mitotane • Nafcillin • Phenobarbital • Phenytoin • Rifabutin • Rifampin • St John's Wort • Troglitazone • Talviraline • Thioridazine
Hypnotics	• Melatonin • Prescribed or OTC
Herbal preparations with sedating effects	• -
Monoamine oxidase inhibitors (MAOIs)	• -
Opioid Analgesics	• -
Muscle relaxants (centrally-acting) with known sedating effects	• GABA analogues • Hydantoins • Phenyltriazines
Other	• Warfarin, heparin, ticlopidine • Systemic isoretinoin • Systemic glucocorticoids

Appendix 3 Extension Phase

Study Design and Plan

The Extension Phase comprises a Maintenance Period of up to 12 weeks in duration, and a Follow-up Period visit that is to occur 4 weeks after the end of the Maintenance Period.

Maintenance Period

During the 12-week Maintenance Period, subjects will continue on the dose of Lemborexant (LEM) that they took at the end of the Titration Period. Subjects will subsequently return to clinic at the visit as specified in the Schedule of Assessments, and will be instructed to return their supply of LEM at each visit. Unused study drug will be collected, and study drug compliance will be assessed. Subjects will be able to discuss changing the dose of LEM at any time during the Maintenance Period, and LEM dose changes may be implemented as clinically determined by the investigator with input from the subject.

Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for all subjects (eg, 4 weeks after the end of the Maintenance Period).

End of Study

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

Study Drug Supplies

Subjects will enter the Extension Phase from the Titration Phase of the Core Study, taking the same dose of LEM that was their final dose of the Titration Phase, ie, LEM5 or LEM10 taken orally in tablet form at night a few minutes before the time the subject intends to try to sleep.

Schedule of Procedures/Assessments

Table 5 presents the Schedule of Procedures and Assessments for the 12-week Extension Phase.

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 - Extension

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				
C-SSRS	X	X	X	X
Prior and concomitant medications	X	X	X	X
Study drug compliance	X		X	X
Dispense study drug				
Retrieve unused study drug	X		X	X
Physical examination[e]	X	X	X	X
Vital signs and weight	X	X	X	X
Clinical laboratory tests[f]	X		X	X
Urine drug screen[g]	X		X	X
Urine pregnancy test[h]	X		X	X
Serum pregnancy test[h,i]				X
12-Lead ECG[j]	X		X	X
Adverse events[k]	X	X	X	X

Table 5 Schedule of Procedures and Assessments in Study E2006-A001-312 - Extension

Phase	Extension			
Period	Maintenance	Follow-up[a]		
Visit	4	5	Early Termination[b,c]	Unscheduled[c, d]
Week	14	18		
Procedures/Assessments				

C-SSRS = Columbia-Suicide Severity Rating Score, ECG = electrocardiogram.

All visits to be done within ±7 days of the schedule.

a: The Follow-up Visit will be conducted 4 weeks after the end of the Extension Phase.
b: Subjects who discontinue study drug prematurely at any time after entering the Extension will be encouraged to return to the site as soon as practicable (preferably within 7 days).
c: During Early Termination and unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.
d: Assessments during an Unscheduled Visit to be conducted at the discretion of the investigator.
e: A full physical examination will be conducted at Visit 4 and 5 and at the Early Termination and Unscheduled Visit at the discretion of the investigator.
f: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
g: Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at Early Termination only for subjects who withdraw because of an adverse event.
h: Female subjects of child-bearing potential only.
i: To be conducted if urine pregnancy testing is positive
j: The ECG should be repeated if a clinically significant abnormality (as determined by the investigator) is observed.
k: 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 9.5.1.5, Adjudication Committee

Statistical Analyses

All statistical analyses will be the responsibility of the Biostatistics Department of Eisai. Statistical programming and analyses will be performed using SAS or other validated software.

Safety Analyses

The primary focus of data summarization for the Extension Phase will be on safety and tolerability. Evaluations of safety data will be performed on the Safety Analysis Set.

The incidence of AEs, out-of-normal-range laboratory test variables, abnormal ECG findings, out-of-range vital signs, and suicidality (C-SSRS) findings, along with changes from baseline in clinical laboratory variables, and vital signs will be summarized by modal dose for Cohort 1 (Intermittent ZOL use) and Cohort 2 (Frequent ZOL use) using descriptive statistics.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-A001-312

Study Protocol Title: A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia

Investigational Product Name: E2006\Lemborexant

IND Number: 111871

SIGNATURES

Authors:

PPD

Date

Eisai, Inc

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-A001-312
Study Protocol Title:	A Multicenter, Pilot Study to Evaluate Next-Dose Transition from Zolpidem to Lemborexant for the Treatment of Insomnia
Investigational Product Name:	E2006\Lemborexant
IND Number:	111871

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International 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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date