Revision History

Previous Version: V7.0
Current Version: V8.0 (per Amendment 06)
Date of Revisions: 13 Aug 2018

Change	Rationale	Affected Section(s)
Updated completed Phase 1 study information	Added results from Study E2006-A001-012	• Section 7.1.2.2.1
Updated list of prohibited concomitant medications	To prohibit the use of moderate cytochrome P450 3A (CYP3A) inhibitors	• Synopsis ○ Concomitant Drug/ Therapy • Section 9.4.7.1 • Section 9.4.7.2 • Appendix 3

Revised summaries for efficacy and safety endpoints in Period 2 to be based on duration of exposure		• Synopsis
		  ○ Secondary Endpoints
		  ○ Exploratory Endpoints
		  ○ Analysis Sets
		  ○ Definitions of Baseline
		  ○ Other Secondary Efficacy and Pharmacodynamic Analyses
		  ○ Exploratory Efficacy and Pharmacodynamic Analyses
		  ○ Safety Analyses
		• Section 9.7.1.1.2
		• Section 9.7.1.1.4
		• Section 9.7.1.2
		• Section 9.7.1.6
		• Section 9.7.1.6.2
		• Section 9.7.1.6.3
		• Section 9.7.1.8
		• Section 9.7.1.8.1
		• Section 9.7.1.8.2
		• Section 9.7.1.8.3
		• Section 9.7.1.8.4
		• Section 9.7.1.8.5

Revised Other Secondary Endpoint Analyses	Added Fatigue Severity Scale analysis	• Synopsis ○ Other Secondary Efficacy and Pharmacodynamic Analyses • Section 9.7.1.6.2

Previous Version: V7.0
Current Version: V8.0 (per Amendment 06)
Date of Revisions: 13 Aug 2018

Change	Rationale	Affected Section(s)
Revised protocol signatories	Corrected signatory for study statistician	• Protocol Signature Page
Correction of typos and spelling errors	Correction	• Revision History • Synopsis ○ Interim Analysis

Previous Version: V6.0 **Current Version: V7.0 (per Amendment 05)** **Date of Revisions: 03 Aug 2018**		
Change	**Rationale**	**Affected Section(s)**
Updated blinding and interim analysis description	Clarify that no interim analysis is being performed and that when all subjects have completed Period 1, all data will be unblinded to the sponsor and that study sites and subjects will remain blinded until the study has been completed.	• Section 2, Synopsis ○ Interim Analysis • Section 9.4.6 • Section 9.7 • Section 9.7.3

Previous Version: V5.0 **Current Version: V6.0 (per Amendment 04)** **Date of Revisions: 28 Jun 2018**		
Change	**Rationale**	**Affected Section(s)**
Corrected typos and redundant text	Correction for consistency	• Synopsis ○ Study Design
Added analysis of Treatment Period 1	Based on the results of pivotal Phase 3 Study E2006-G000-304 and special safety studies, Eisai decided to include a database lock with interim analysis to assess efficacy in the double-blind placebo-controlled treatment period. All available safety data will also be assessed	• Synopsis ○ Interim Analysis • Section 9.7 • Section 9.7.3
Revised blinding statement	In the event of an interim analysis, Sponsor staff will be unblinded; however, site personnel, investigator, and subjects will remain blinded	• Section 9.4.6
Revised information about study signatories	Correction	• Protocol Signature Page

Updated analysis sets and analysis plan	To align with Regulatory Authority provision (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E9 Addendum)	• Synopsis
		  ○ Analysis Sets
		  ○ Analysis of Primary Endpoint
		• Section 9.7.1.2
		• Section 9.7.1.6.1

Previous Version: V4.0
Current Version: V5.0 (per Amendment 03)
Date of Revisions: 06 Mar 2017

Change	Rationale	Affected Section(s)
Revised approximate number of sites from 110 to 125	To facilitate study enrollment	• Synopsis – Site(s) • Section 6 • Figure 1
Revised to Screening Period from up to -28 days to up to -35 days	To allow flexibility in scheduling	• Synopsis – Study Design • Section 9.1 • Section 9.1.1.1 • Table 3
Revised the requirement for a history of "difficulties with sleep onset and sleep maintenance" to "difficulties with sleep onset and/or sleep maintenance"	To permit broader inclusion of appropriate subjects	• Synopsis – Study Design • Section 9.1 • Section 9.1.1.1 • Section 9.2.4
Deleted "or early morning awakening" from the requirements.	Early morning awakening is not an inclusion criterion.	• Synopsis – Study Design • Section 9.1.1.1
Deleted the Munich Parasomnia Scale (MUPS) and revised text such that investigators will instead interview subjects regarding possible history of parasomnias.	To bring more efficiency to screening for parasomnias, by allowing investigators to use interview to screen for a history of REM-behavior disorder sleep-eating, or sleep-related violent behaviour, and use clinical judgement, rather than automatically excluding subjects who endorse these items on the MUPS scale.	• Synopsis – Study Design • Synopsis – Exclusion Criteria • Synopsis – Assessments • Section 4 • Section 9.1.1.1 • Section 9.3.2 • Section 9.5.1.2.2 • Table 3
Revised inclusion (#3,7, & 10) from sSOL ≥30 AND sWASO ≥60 minutes to sSOL ≥30 minutes AND/OR sWASO ≥60 minutes.	To permit broader inclusion of appropriate subjects	• Synopsis – Inclusion Criteria • Section 9.3.1
Revised inclusion (#5) for regular bedtime from between 21:00 and 24:00 to between 21:00 and 01:00, waketime from between 05:00 and 09:00 to between 05:00 and 10:00	To permit broader inclusion of appropriate subjects	• Synopsis – Inclusion Criteria • Section 9.3.1
Revised inclusion (#8) requiring the subjects has a regular time spend in bed, either sleeping or trying to sleep, between 7 and 10 hours		• Synopsis – Inclusion Criteria • Section 9.3.1
Revised inclusion (#9) requiring maximum duration of time spent in bed from 9 hours to 10 hours, on	To permit broader inclusion of appropriate subjects	• Synopsis – Inclusion Criteria • Section 9.3.1

Previous Version: V4.0
Current Version: V5.0 (per Amendment 03)
Date of Revisions: 06 Mar 2017

Change	Rationale	Affected Section(s)
Sleep Diary at Visit 2a		
Revised inclusion (#11) requiring reconfirmation of regular bedtimes and waketimes during Run-In Period	To permit broader inclusion of appropriate subjects	• Synopsis – Inclusion Criteria • Section 9.3.1
Revised inclusion (#12) to delete requirement for no more than 2 nights with duration of time in bed >9 hours in Run-In	To permit broader inclusion of appropriate subjects	• Synopsis – Inclusion Criteria • Section 9.3.1
Revised inclusion (#13) "TIB" to "staying in bed"	For clarity.	• Synopsis – Inclusion Criteria • Section 9.3.1
Revised exclusion (#1) from ESS score ">10" to ">15" as an indicator of excessive daytime sleepiness, and require that scores of 11 to 15 be recorded as excessive daytime sleepiness in subject's Medical History)	To avoid low specificity of more stringent criterion, and to record excessive sleepiness in medical history instead of excluding subjects	• Synopsis – Exclusion Criteria • Section 9.3.2 • Section9.5.1.2.1
Revised exclusion (#3) to remove MUPS assessment and allow evaluation based upon reporting of a history of sleep-related violent behavior or sleep driving, or any other complex sleep-related behavior (eg, making phone call or preparing and eating food while sleeping)	To permit broader inclusion of appropriate subjects	• Synopsis – Exclusion Criteria • Section9.3.2
Revised exclusion (#9) for females of CBP from "…30 days before study entry *and*…" to "…30 days before study entry *or* …"	For clarity	• Synopsis – Exclusion Criteria • Section9.3.2
Revised exclusion (#15) from "A prolonged QT/QT interval (QTc >450 ms)" to "A prolonged QT/QT interval corrected by Fridericia's formula (QTcF) >450 ms"	For clarity and correction of error.	• Synopsis – Exclusion Criteria • Section9.3.2 • Section9.5.1.5.1
Revised exclusion (#20) for suicidal behavior as per the C-SSRS from "lifetime" to "in the past 10 years"	To facilitate enrollment and align with other protocols in the program	• Synopsis – Exclusion Criteria • Section9.3.2
Revised exclusion (#21) to specify major surgery.	To allow for the possibility of minor surgery that will not interfere with study assessments	• Synopsis – Exclusion Criteria • Section9.3.2
Revised definition of sSE	For clarity	• Synopsis – Assessments • Section 9.5.1.3.1
Revised name and description of	As requested by FDA, to	• Synopsis – Study Design

Previous Version: V4.0
Current Version: V5.0 (per Amendment 03)
Date of Revisions: 06 Mar 2017

Change	Rationale	Affected Section(s)
Adjudication Committee, and added seizures as adverse events to be adjudicated	include information on seizures for adjudication as symptoms of cataplexy	• Synopsis – Statistical Methods • Section9.2.3
Added requirement to question subjects as to whether they have had a fall, at each visit, and record supplemental information	As requested by FDA.	• Table 3
Revised analyses for Primary, Secondary and Exploratory Efficacy	To align with regulatory recommendations for handling missing data	• Synopsis – Statistical Methods • Section 9.7.1.6.1 • Section 9.7.1.6.2 • Section 9.7.1.6.3
Deleted text related to the Symptoms of Narcolepsy Screen	Correction of error. This screen is not employed in the study.	• Section 9.5.1.2.2
Provided window around Visits 6 through 15.	To correct the omission.	• Table 3
Revised definitions of prior and concomitant medications	To allow separate analyses for the Run-In Period, Treatment Period 1, and Treatment Period 2.	• Section 9.7.1.5
Revised text regarding ECG interpretation categories	For clarity	• Section 9.7.1.8.5
Revised T-BWSQ assessment description such that scores above 20 will not be considered clinically significant and that the symptoms will no longer be summarized separately from all other AEs.	For clarity	• Synopsis – Study Assessments • Section 9.5.1.5.7
Revised List of Prohibited Concomitant Medications	To correct lists of strong CYP3A inhibitors and CYP3A inducers	• Appendix 3
Added the requirement of a Data Safety Monitoring Board	Per the request of FDA	• Synopsis – Study Design • Section 9.2.3
Converted Month 2 visit from phone to in-person visit.	Per the request of FDA	• Synopsis – Study Design • Section 9.1.2.1 • Table 3

Previous Version: V3.0 **Current Version: V4.0 (per Amendment 02)** **Date of Revisions: 25 Oct 2016**		
Change	**Rationale**	**Affected Section(s)**
Revised exclusion criteria regarding highly effective forms of contraception	Per VHP feedback	• Synopsis: Exclusion Criteria • Section 9.3.2
Revised Sleep Diary to Sleep Diary	Correction of typographical error	• Synopsis: Additional Secondary Endpoints • Section 9.7.1.1.2
Revised inclusion and exclusion criteria to be checked at Screening and Baseline	Correction of errors	• Appendix 2

Previous Version: V2.0 (revised protocol)
Current Version: V3.0 (per Amendment 01)
Date of Revisions: 29 Sep 2016

Change	Rationale	Affected Section(s)
Deleted colon after "Evaluate the safety and tolerability of LEM5 and LEM10"	Correction of error	• Synopsis: Objectives • Section 8.2.
Stated that enrollment of subjects <65 years may be limited if the percentage of enrolled subjects ≥65 years is below expectations toward the end of the study	To ensure that approximately 40% of subjects are age 65 years or older	• Synopsis: Study Design • Section 9.1
Revised "from Screening through end of Treatment Period" to "from Screening to the EOS Visit" for urine drug testing	Correction of error	• Synopsis: Study Design
Clarified that subjects who discontinue study medication but do not agree to return for study visits will undergo an EOS visit	Clarification and correction; the term "Follow-up Visit" is not used elsewhere in the protocol	• Synopsis: Study Design • Section 9.5.2 • Section 9.5.5
Clarified the dates that the study will begin and end enrollment	Clarification	• Synopsis: Study Design. • Section 9.1.
Clarified the term abstinence	Clarification as required by the VHP	• Synopsis: Exclusion Criteria • Section 9.3.2
Clarified excessive caffeine use	Clarification as required by the VHP	• Synopsis: Exclusion Criteria • Section 9.3.2
Clarified that subjects who lack capacity and/or whose cognitive decline indicates disorientation to person/place/time and/or situation are excluded	Clarification as required by the VHP	• Synopsis: Exclusion Criteria • Section 9.3.2
Revised the washout interval between taking a prohibited medication and the 1st dose of study medication	Correction of inconsistency between text (incorrect) and Exclusion Criteria (correct)	• Synopsis: Concomitant Drug/Therapy • Section 9.4.7.2
Specified that the statistical model will include region if necessary, that countries with small numbers of subjects may be pooled by region, and that regions will be grouped in consideration of the number and homogeneity of subjects from each region	Clarification/specification as required by the VHP	• Synopsis: Statistical Methods • Section 9.7.1.6.1

Previous Version: V2.0 (revised protocol)
Current Version: V3.0 (per Amendment 01)
Date of Revisions: 29 Sep 2016

Change	Rationale	Affected Section(s)
Relocated definition of SAP	Editorial quality	• Synopsis, Statistical Methods
Specified that informed consent will be taken by personnel in accordance with national legislation	Specification required by the VHP	• Section 5.3
Clarified the reason why subjects should not eat a meal within 3 hours before taking the study drug	Clarification as required by the VHP	• Section 9.4.5
Deleted the statement that dose adjustment of an allowable medication is permitted for those drugs where monitoring and dose modulation are typical practice	Correction of error: dose modulation of all concomitant medications is permitted during the study.	• Section 9.4.7.2
Specified that the neurological examination must be conducted by a clinician whose clinical experience ensures that an adequate assessment of domains underlying the exclusion criteria can be performed	Specification as required by the VHP	• Section 9.5.1.2.1
Deleted pharmacokinetic sample at EOS visit from Table 2.	Correction of error: No PK sample with be taken at EOS	• Section 9.5.1.5.3
Clarified that clinical lab tests and/or PK sampling will also be conducted at ET/EDD visits	Clarification	• Section 9.5.1.5.3
Added visit number, physical examination, vital signs, weight, ECG, urine pregnancy test, and clinical laboratory tests to the EOS visit	Clarification. This information was previously in the footnote but not in the table.	• Section 9.5.2
Deleted "ISI – Insomnia Severity Index" from abbreviations	Correction of duplication	• Section 9.5.2
Specified that EOS must be conducted within ± 7 days of the schedule	Correction of error. The EOS, not the ET, must be conducted within this timeframe.	• Section 9.5.2
Clarified that the maximum duration Run-In Period must be 17 days.	Clarification	• Section 9.5.2

Previous Version: V2.0 (revised protocol)
Current Version: V3.0 (per Amendment 01)
Date of Revisions: 29 Sep 2016

Change	Rationale	Affected Section(s)
Specified that inclusion and exclusion criteria that must be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2	Clarification	• Section 9.5.2
Deleted Symptoms of Narcolepsy Screen from Sleep Disorders Screening Battery	Correction of error	• Section 9.5.2
Specified that study drug compliance (tablet count) will be carried out at each clinic visit from Visit 3a through Visit 15	Clarification	• Section 9.5.2
Replaced Xs with a broken arrow to indicate timepoints for prior and concomitant medications sleep diary, and adverse event collection	For clarity	• Section 9.5.2
Renumbered superscripts that indicate footnotes	For consistency between superscripts and the footnotes to which they refer.	• Section 9.5.2
Delete “only” from footnote “u” (instructions for PK sampling at ET)	Correction of error (PK sampling will also take place at other time points)	• Section 9.5.2
Specified that the investigator agrees to allow direct access to source documents and study facilities to sponsor representative(s), monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative	Specification required by the VHP.	• Section 11.5
Revised the lists of strong CYP3A inhibitors and CYP3A inducers	Correction of errors.	• Appendix 3

Previous Version: V1.0 (original protocol)
Current Version: V2.0 (revised protocol)
Date of Revisions: 15 Jul 2016

Change	Rationale	Affected Section(s)
Deleted requirement that a blood sample be taken at end of study for determination of lemborexant blood levels	Correction of error	• Synopsis – Study Design • Section 9.1.2.4
Clarified that reconfirmation of bedtimes take place for the final 7 nights of the Run-in Period	For clarity and consistency	• Synopsis – Inclusion Criteria • Section 9.3.1
Specified that exclusion criteria include current diagnosis of obstructive sleep apnea (CPAP)	For clarity	• Synopsis – Exclusion Criteria • Section 9.3.2
Revised STOPBang score cutoff for exclusion from study	To avoid low specificity of more stringent criterion	• Synopsis – Exclusion Criteria • Section 9.3.2
Revised Epworth Sleepiness Scale score cutoff for exclusion from study	To avoid low specificity of more stringent criterion	• Synopsis – Exclusion Criteria • Section 9.3.2
Provided examples of clinically significant disease that would exclude the subject from the study	For clarity	• Synopsis—Exclusion Criteria • Section 9.3.2
Stated that subjects taking sedating drugs that would interfere with occupation or activities will be excluded	To exclude such individuals from the study for reasons of safety	• Synopsis – Exclusion Criteria • Section 9.3.2
Revised the washout interval between taking a prohibited medication, including treatment for insomnia, and the 1st dose of study medication	For consistency and to account for medications or insomnia treatments with long half-lives	• Synopsis – Exclusion Criteria • Section 9.3.2
Added wording to clarify prohibitions on concomitant drugs during study	Clarification	• Synopsis – Concomitant Drug Therapy • Section 9.4.7.2
Changed wording such that sleep diary will ask, not determine, alcohol consumption	For accuracy	• Synopsis – Assessments • Section 9.5.1.3.1
Allowed flexibility for the means of documenting the time and date of 2 most recent doses before each blood sample for pharmacokinetic analyses	Time and date are being documented by means other than in the electronic Case Report Form	• Synopsis – Assessments • Section 9.5.1.4.1 • Table 3 (footnote “r”)

Change	Rationale	Affected Section(s)
Revised method for assessment of rebound insomnia	To emphasize assessment of rebound insomnia at individual subject level	• Synopsis – Statistical Methods • Section 9.7.1.6.2
Provided that for applicable countries, the year of birth will be collected instead of the date of birth	To meet requirements in some countries regarding personally identifying information	• Section 9.5.1.1
Specified viral tests for hepatitis B and hepatitis C	To provide additional detail of screening assessments	• Section 9.5.1.5.3 • Table 3 (footnote "n")
Deleted alcohol and nicotine/ cotinine from screening for drugs of abuse	To correct an error, as these drugs are not being tested in the urine drug screen in this study	• Section 9.5.1.5.3
Corrected window of study days for Screening	To correct an error	• Figure 1 • Table 3
Clarified interval for reporting of follow-up SAE, pregnancy, or breastfeeding information	For clarity	• Section 9.5.4.1 • Section 9.5.4.2
Added sentence distinguishing between definitions of "study completer" per protocol versus for statistical analysis purposes	For clarity	• Section 9.5.5
Deleted reference to examples of source documents that will not be used in this study	For accuracy	• Section 11.3
Deleted glucose-metabolizing agents from list of prohibited/concomitant medications	This prohibition is considered unnecessary.	• Appendix 3

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-G000-303
Study Protocol Title:	A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel-Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E2006/lemborexant
Indication:	Insomnia disorder
Phase:	Phase 3
Approval Date:	V1.0 Final, 29 Apr 2016 (original protocol) V2.0 Final, 15 Jul 2016 (revised protocol) V3.0 Final, 29 Sep 2016 (per Amendment 01) V4.0 Final, 25 Oct 2016 (per Amendment 02) V5.0 Final, 06 Mar 2017 (per Amendment 03) V6.0 Final, 28 Jun 2018 (per Amendment 04) V7.0 Final, 03 Aug 2018 (per Amendment 05) V8.0 Final, 13 Aug 2018 (per Amendment 06)
IND Number:	111871
EudraCT Number:	2015-001463-39
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2006/lemborexant

Name of Active Ingredient: (1R,2S)-2-{[(2,4-Dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide

Study Protocol Title

A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel-Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder

Investigator(s)

To be determined

Site(s)

Approximately 125 investigational sites in North America, South America, Europe, Asia, and Oceania (revised per Amendment 03)

Study Period and Phase of Development

Approximately 30 months

Phase 3

Objectives

Primary Objective

Determine the efficacy of lemborexant 5 mg (LEM5) and 10 mg (LEM10) compared to placebo (PBO) on subjective sleep onset latency (sSOL) after 6 months of treatment in subjects with insomnia disorder

Key Secondary Objectives

- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective sleep efficiency (sSE) after 6 months of treatment in subjects with insomnia disorder
- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective wake after sleep onset (sWASO) after 6 months of treatment in subjects with insomnia disorder

Additional Secondary Objectives

- Determine the efficacy of LEM5 and LEM10 compared to PBO on sSOL, sSE, sWASO, and subjective total sleep time (sTST):
  - over the 1st 7 nights of treatment
  - after 1 month of treatment
  - after 3 months of treatment
- Determine the efficacy of LEM5 and LEM10 compared to PBO on sTST at 6 months
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to PBO as defined by response on sSOL or sWASO at 6 months and 12 months

- Evaluate the safety and tolerability of LEM5 and LEM10
- Evaluate the efficacy of LEM5 and LEM10 compared to PBO as measured by responses on the Insomnia Severity Index (ISI) and the Fatigue Severity Scale (FSS) after 6 months
- Evaluate rebound insomnia following discontinuation of treatment
- Evaluate morning sleepiness during and following completion of treatment
- Evaluate persistence of efficacy of LEM5 and LEM10 over 12 months

Exploratory Objectives

The following will be explored for both LEM5 and LEM10 compared to PBO over Treatment Period 1 (Period 1) and over Treatment Period 2 (Period 2) with analyses dependent on whether subjects received active treatment or PBO during Period 1. (revised per Amendment 04)

- Efficacy on quality of sleep
- Health outcomes on the EuroQOL version 5D-3L (EQ-5D-3L), Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH), and Patient Global Impression – Insomnia (PGI-Insomnia)
- Efficacy on sSOL, sSE, sWASO, sTST, ISI, and FSS
- Withdrawal symptoms after completion of treatment (Period 2 only)

The following will be explored for LEM5 and LEM10:

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Population pharmacokinetic (PK) modeling for lemborexant
- PK/pharmacodynamic (PD) relationships between lemborexant concentrations and efficacy and safety variables

Study Design

E2006-G000-303 is a 12-month, multicenter, randomized, controlled, double-blind, parallel-group study of 2 doses of lemborexant in approximately 900 male or female subjects with insomnia disorder. Approximately 40% of the population will be 65 years of age or older. Note: enrollment of subjects <65 years may be limited if the percentage of enrolled subjects ≥65 years is below expectations toward the end of the study. (revised per Amendment 01)

The study will have 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods that will last up to 35 days: a Screening Period, a Run-In Period and a Baseline Period. The Randomization Phase will comprise a 6-month, placebo-controlled treatment period (Period 1). During the next 6 months (Period 2), subjects will receive only active treatment. Subjects will be informed that they will receive PBO at some point during the study and that all will receive active drug for at least 6 months. They will not be informed of either the timing of these periods or the timing of the 2nd randomization. A 2-week Follow-Up Period will then take place, followed by an End of Study Visit (EOS). (revised per Amendment 03)

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding adverse events (AEs), 12-lead electrocardiograms (ECGs), vital signs, weight, height (once at Visit 1), clinical hematology and chemistry analysis and urinalysis, and suicidality, assessed using an electronic version of the Columbia-Suicide Severity Rating Scale (eC-SSRS). At each visit from Screening to the EOS Visit,

subjects will also undergo a urine drug screen. (revised per Amendment 01)

Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the 1st Screening Visit (Visit 1), informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject has a history of difficulties with sleep onset and/or sleep maintenance. Screening assessments will include the ISI, and the Epworth Sleepiness Scale (ESS), the STOPBang, and the International Restless Legs Scale (IRLS) the latter 3 assessments collectively called the Sleep Disorders Screening Battery (SDSB). The FSS and health-related quality-of-life measures the EQ-5D-3L and the WPAI-GH will be administered. Additional eligibility criteria will be assessed and safety assessments will be conducted. (revised per Amendment 03)

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

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, provided that the Sleep Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the 2nd Screening Visit (Visit 2a). Subjects will return to the clinic and eligibility criteria will be determined. Subjects who are not eligible based on Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment. Visit 2a must occur between Day -17 and Day -14. A urine drug test will be performed. Subjects who continue to meet eligibility criteria will then receive PBO (single-blind) sufficient for 14 nights and will enter the Run-In Period which will last approximately 14 nights and a maximum of 17 nights.

Run-In Period

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

Baseline Period (Study Baseline)

On Day 1, the Run-In Period will end and the Baseline Period will begin. Subjects will return to the clinic for this visit (Visit 3), and the ISI will be administered. If subjects remain eligible, the FSS, EQ-5D-3L, and WPAI-GH will then be administered. Blood and urine samples will be collected for routine safety assessment, suicidality will be assessed using the eC-SSRS, and a urine drug test will be performed. An ECG will be performed, and vital signs and weight will be assessed. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized and begin the Treatment Period.

Treatment Period (Periods 1 and 2)

Treatment Periods 1 and 2 (Periods 1 and 2) will begin on Day 1 and will continue for 12 months.

Subjects will be randomized, in a double-blind manner, to receive LEM5 or LEM10, or PBO (approximately 1:1:1, stratified by country and age group (<65 years old; ≥65 years old). Study drug will be dispensed and subjects will be provided with instructions to continue completing the Sleep Diary and taking study drug daily at home according to the same schedule and with the same restrictions as during the Run-In Period.

Period 1 will begin with the 1st dose of randomized study medication.

At the end of Month 6 (Period 2 Baseline), subjects who received PBO during Period 1 will undergo a 2nd randomization to receive either LEM5 or LEM10 (approximately 1:1, stratified by country and age group (<65 years old; ≥65 years old) during Period 2. Subjects who received lemborexant during Period 1 will continue to receive lemborexant at the same dose level during Period 2. Subjects will not be informed of the timing of the 2nd randomization (at the end of Month 6); allocation of dose will be double-blind. (revised per Amendment 04)

Subjects will continue to complete the Sleep Diary every morning throughout both Periods 1 and 2. They will return to the clinic at the end of Months 1, 2, 3, 6, 9, and 12. At each clinic visit, safety and tolerability will be assessed, including assessment of AEs, and a urine drug test will be carried out. At each clinic visit, except Month 12, the Sleep Diary will be reviewed for completeness, compliance will be check, and study drug will be dispensed. At months 1, 3, 6, 9, and 12 the eC-SSRS will be administered. At the end of Months 1, 3, 6, 9, and 12, the ISI, FSS, the EQ-5D-3L and the PGI-Insomnia will be completed. At the end of Months 3, 6, 9 and 12, the WPAI-GH will also be completed. At predefined visits, a blood sample will be collected for PK analysis. (revised per Amendment 03)

At the end of Months 4, 5, 7, 8, 10, and 11, the site will telephone the subject to assess AEs, record concomitant medications, and review Sleep Diary entries. If any AE is clinically significant and requires follow-up, an Unscheduled Visit should be arranged as soon as possible. (revised per Amendment 03)

Period 2 will end with the completion of the 12-month visit. For analysis purposes, a subject who completes assessments through Period 2 will be considered to have completed the study.

Follow-up Period

The Follow-up Period will begin at the end of Period 2. Subjects will discontinue study drug but will continue to complete the Sleep Diary each morning until the EOS visit.

Premature Discontinuation of Study Drug

The subject may elect to discontinue the study at any time for any reason. Subjects who discontinue study drug prematurely at any time after randomization at Visit 3 (Study Baseline) will be encouraged to return to the site as soon as practicable (preferably within 7 days). These subjects will be encouraged to continue to complete all study assessments (excepting PK samples, which will not be taken), including the Sleep Diary, and to return for all subsequent clinic visits, without the administration of study medication.

Subjects who do not agree to this will undergo an Early Termination (ET) Visit and the EOS visit, as described in the Schedule of Procedures/Assessments. (revised per Amendment 01) Subjects who agree will undergo an Early Drug Discontinuation (EDD) Visit, during which all assessments will be conducted that would be made at an ET visit. These subjects need not attend the next regularly

scheduled visit if this falls within the visit window of the next visit. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled visits.

Adjudication Committee (revised per Amendment 03)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [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. (revised per Amendment 03)

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination of whether the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 03)

End of Study

At least 14 days but no more than 18 days after the Treatment Period, subjects will return to the clinic for the EOS Visit. At the EOS Visit, in addition to standard safety assessments and the eC-SSRS, a urine drug test will be conducted, the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) will be administered and sleep diaries will be collected. After the End of Study Visit, subjects' participation in the study will be finished.

Additional Study Information

The end of the study will be the date of the last study visit for the last subject. As required by some regulatory agencies, the following estimates are provided:

- The study will begin enrollment in approximately November 2016 (revised per Amendments 01 and 03)
- The estimated duration for each subject on study is anticipated to be a maximum of 60 weeks (a maximum 35-day Prerandomization Phase [that includes a Screening Period, a maximum 17-day Run-In Period, and a Baseline Period] + 52 weeks of the Randomization Phase + a 1-week window + a 2-week Follow-Up Period). (revised per Amendment 03)
- Approximately 900 subjects with insomnia disorder (18 years or older) will be randomized to receive LEM5 or LEM10 or PBO for 6 months. After 6 months, subjects who previously received lemborexant will continue to receive lemborexant at the same dosage level for an additional 6 months, while subjects who previously received PBO will undergo a 2nd randomization to receive LEM5 or LEM10 for 6 months.

Number of Subjects

Approximately 1500 subjects will be screened to provide 900 randomized subjects.

Inclusion Criteria

1. Male or female, age 18 years or older at the time of informed consent
2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep in the form of difficulty getting to sleep, difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of sSOL ≥30 minutes on at least 3 nights per week in the previous 4 weeks AND/OR sWASO ≥60 minutes on at least 3 nights per week in the previous 4 weeks (revised per Amendment 03)
4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At 1st Screening Visit (Visit 1) and 2nd Screening Visit (Visit 2a): Reports regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00 (revised per Amendment 03)
6. At Screening and Study Baseline: ISI score ≥15
7. At the 2nd Screening Visit (Visit 2a): Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary completed on at least 7 consecutive mornings (minimum 5 of 7 for eligibility), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 03)
8. At 2nd Screening Visit (Visit 2a): Confirmation of regular bedtimes and waketimes, as determined from responses on the Sleep Diary completed on a minimum of 7 consecutive mornings between the 1st and 2nd screening visit, such that the subject has a regular time spend in bed, either sleeping or trying to sleep, between 7 and 10 hours (revised per Amendment 03)
9. At the 2nd Screening Visit (Visit 2a): Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary completed on 7 mornings between the 1st and 2nd screening visit, such that there are not more than 2 nights with duration of time spent in bed <7 hours or >10 hours (revised per Amendment 03)
10. At Baseline (Visit 3a): Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary for the final 7 nights of the Run-in Period, such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 03)
11. At Baseline (Visit 3a): Confirmation of regular bedtimes and waketimes,, such that the subject has a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours for the final 7 nights of the Run-In Period (revised per Amendment 03)

12. At Baseline (Visit 3a): Reconfirmation of regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00, for the final 7 nights of the Run-In period (revised per Amendment 03)
13. Willing and able to comply with all aspects of the protocol, including staying in bed at least 7 hours each night (revised per Amendment 03)
14. Willing to not start a behavioral or other treatment program for insomnia during the subject's participation in the study

Exclusion Criteria

1. A current diagnosis of sleep-related breathing disorder, including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on the SDSB as follows:
   - STOPBang score ≥5
   - IRLS score ≥16
   - ESS score >15 (Scores of 11-15 require that excessive daytime sleepiness must be recorded in subject's Medical History) (revised per Amendment 03)
2. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicate the need for referral for a diagnostic evaluation for the presence of narcolepsy.
3. Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior (eg, making phone call or preparing and eating food while sleeping) (revised per Amendment 03)
4. For subjects who underwent diagnostic polysomnography (PSG) within 1 year before informed consent:
   - Age 18 to 64 years: Apnea-Hypopnea Index ≥10, or Periodic Limb Movements with Arousal Index ≥10
   - Age ≥65 years: Apnea-Hypopnea Index >15, or Periodic Limb Movements with Arousal Index >15
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening
6. Beck Anxiety Inventory (BAI) score >15 at Screening
7. Habitually naps more than 3 times per week
8. Females who are breastfeeding or pregnant at Screening or Study Baseline (as documented by a positive serum beta-human chorionic gonadotropin [ß-hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
9. Females of childbearing who:
   - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, injectable contraceptives, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 28 days after study drug discontinuation. Periodic abstinence (e.g., calendar, ovulation,

symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. (revised per Amendments 01, 02, and 03)

- Are currently abstinent, and do not agree to use a highly effective method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation. (revised per Amendment 02)
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation.

(NOTES: All females will be considered to be of childbearing 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].

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.) (revised per Amendment 02)

10. Excessive caffeine use that in the opinion of the investigator contributes to the subject's insomnia, or habitually consumes caffeine-containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and ≥5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation. To be exclusionary, those symptoms must cause distress or impairment in social, occupational and other forms of functioning, and not be associated with other substance, mental disorder or medical condition. (revised per Amendment 01)
11. History of drug or alcohol dependency or abuse within approximately the previous 2 years
12. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to 2 or fewer drinks per day or forego having alcohol within 3 hours before bedtime for the duration of his/her participation in the study
13. Known to be human immunodeficiency virus (HIV) positive
14. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
15. A prolonged QT/QT interval corrected by Fridericia's formula (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms) (revised per Amendment 03)
16. Current evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; severe hepatic insufficiency; gastrointestinal; renal including severe renal impairment; neurological [including subjects who lack capacity and/or whose cognitive decline indicates disorientation to person/place/time and/or situation] or psychiatric disease or malignancy within the past 5 years [other than adequately treated basal cell carcinoma]) or chronic pain that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects

for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. (revised per Amendment 01)

17. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
18. Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
19. Any suicidal ideation with intent with or without a plan at Screening or Study Baseline or within 6 months of Study Baseline (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)
20. Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS) (revised per Amendment 03)
21. Scheduled for major surgery during the study (revised per Amendment 03)
22. Used any prohibited prescription or over-the-counter medications within 1 week or 5 half lives, whichever is longer, before the 1st dose of study medication (Run-In Period). (A list of prohibited or limited concomitant medications is presented in Appendix 3 of the protocol.)
23. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana, within 1 week or 5 half lives, whichever is longer, before the 1st dose of study medication (Run-In Period)
24. Failed treatment with suvorexant (efficacy or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
25. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Study Baseline
26. A positive drug test at Screening, Run-In, or Baseline or unwilling to refrain from use of recreational drugs during the study
27. Hypersensitivity to the study drug or any of the excipients
28. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5 times the half-life, whichever is longer preceding informed consent
29. Previously participated in any clinical trial of lemborexant

Study Treatments

LEM5, LEM10, or lemborexant-matched PBO taken orally in tablet form each night immediately before the time the subject intends to try to sleep

Run-In Period

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

Randomization Phase (Periods 1 and 2)

During Period 1 (Day 1 through end of Month 6), all subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized:

- LEM5: 1 lemborexant 5-mg tablet
- LEM10: 1 lemborexant 10-mg tablet

- PBO: 1 lemborexant-matched PBO tablet

During Period 2 (Month 7 through 12), all subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized

- LEM5: 1 lemborexant 5-mg tablet
- LEM10: 1 lemborexant 10-mg tablet

Duration of Treatment

A maximum of approximately 55.5 weeks: Up to 17 days of PBO during the Run-In Period and up to 52 weeks of randomized treatment.

Concomitant Drug/Therapy

Caffeine will be permitted in limited quantities during the study. Subjects will be instructed to limit caffeine consumption to ≤4 cups of caffeinated beverages per day, or ≤400 mg caffeine per day. Subjects will be instructed to avoid caffeine after 18:00 on all days during the study.

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcohol-containing drinks on any given day while in the study, and will be instructed not to consume any alcohol within 3 hours before bedtime. Because the definition of a standard drink varies among countries and regions, no definition of the volume or alcohol content of a standard drink is provided, with the exception of Japan. For sites and subjects in Japan, a drink will be defined as 360 mL of beer, 150 mL of wine, or 50 mL of liquor. Compliance with these restrictions will be monitored by specific questions in the Sleep Diary. If subjects cannot comply after counseling, they may be discharged from the study.

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

Prohibited medications include strong and moderate cytochrome P450 (CYP3A) inhibitors and all CYP3A inducers. Prohibited therapies also include: any treatment for insomnia disorder, including any drugs or nonpharmacological treatment such as cognitive behavioral therapy; medications that are used for the purpose of inducing sleep (hypnotics) or inducing wakefulness (stimulants; except caffeine; see above) and medications that have known sedating effects or alerting effects. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants). (revised per Amendment 06)

If a medication is not on the list of prohibited medications but, in the opinion of the investigator, causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in Appendix 3 of the protocol, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted.

If a subject starts any prohibited medication or therapy, 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 CYP3A4 inducers will not be permitted at any time for any duration during the study. (revised per Amendment 06)

Assessments

Screening Assessments (administered only at the 1st screening visit)

Sleep Disorders Screening Battery (SDSB) (revised per Amendment 03)

The SDSB will include the following, to be self-administered: (revised per Amendment 03)

- STOPBang: a list of 8 questions to be answered Yes or No, which screens subjects for obstructive sleep apnea
- IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome
- ESS: a questionnaire that rates the probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, which assesses the severity of daytime sleepiness

Beck Depression Inventory – II

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

Beck Anxiety Inventory

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

Efficacy Assessments

Electronic Sleep Diary

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through theFollow-Up Period. This Sleep Diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy. In addition, the Sleep Diary will include questions that relate to morning sleepiness and to alcohol consumption. (revised per Amendment 03)

Sleep Parameters

- sSOL: estimated minutes from the time the subject attempted to sleep until sleep onset
- sWASO: sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night
- sTST: derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
- sSE: proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reported attempting to sleep until the time the subject stopped trying to sleep for the night, and time spent asleep derived from time spent in bed minus sWASO (revised per Amendment 03)

Quality of Sleep and Morning Sleepiness

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

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

Alcohol Consumption

The Sleep Diary will include questions that ask about alcohol consumption the previous day, including within 3 hours before bedtime and/or exceeding the daily maximum of 2 alcoholic drinks per day.

ISI

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

FSS

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

Pharmacokinetic Assessments

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

Pharmacodynamic Assessments

There are no assessments that are primarily PD. For purposes of PK/PD modeling, selected efficacy and safety assessments will be used in lieu of PD assessments.

Safety Assessments

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

eC-SSRS

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

T-BWSQ

An assessment of withdrawal symptoms will be made using the T-BWSQ completed at the End of Study visit. Subjects will be asked about the presence/absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score=0), "Yes – moderate" (Score=1) or "Yes – severe" (Score=2). The sum of responses will be the subject's score. (revised per Amendment 03)

Other Assessments

EQ-5D-3L

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

Patient Global Impression (PGI) – Insomnia

The PGI-Insomnia is a self-report assessment asking about a subject's perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a: helped/worsened sleep, b: decreased/increased time to fall asleep, and c: increased/decreased total sleep time) and 1 item related to perceived appropriateness of study medication strength. The 1st 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).

Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH)

The WPAI-GH collects data on absenteeism and presenteeism. The scale comprises 6 items that are used to create the 4 scores shown below. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

- Percent work time missed due to health
- Percent impairment while working due to health
- Percent overall work impairment due to health
- Percent activity impairment due to health

Bioanalytical Methods

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

Statistical Methods

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

Where Sleep Diary endpoints are described, the time points refer to the mean of the final 7 nights before the visit unless otherwise stated. The following endpoints will be analyzed for LEM5 and LEM10 compared to PBO.

Primary Endpoint

Mean change from Study Baseline in sSOL at Month 6

Secondary Endpoints

Key Secondary endpoints:

- Mean change from Study Baseline in sSE at Month 6
- Mean change from Study Baseline of sWASO at Month 6

Additional Secondary Endpoints:

- Mean change from Study Baseline of sSOL, of sSE, of sWASO and of sTST, at the beginning of treatment (mean of the 7 nights after the 1st dose in Period 1), at Month 1 and at Month 3
- Mean change from Study Baseline of sTST at Month 6
- Proportion of responders at Month 6 and Month 12, where sleep onset responder is defined as follows: sSOL at Study Baseline is ≥30 minutes and mean sSOL at 6 months is ≤20 minutes, and sleep maintenance responder is defined as follows: sWASO at Study Baseline is ≥60 minutes and mean sWASO at 6 months is ≤60 minutes and shows a reduction of >10 minutes compared to Study Baseline.
- Change from Study Baseline in daytime functioning, assessed as the total score from the 4 items on daytime functioning, on the ISI, at Months 1, 3, and 6
- Change from Study Baseline on the FSS at Months 1, 3, and 6
- Ratings on the morning sleepiness item of the Sleep Diary, for:
  - The mean change from Study Baseline of the 1st 7 mornings after the 1st dose in Period 1 and Period 2
  - The mean change from Study Baseline at: Month 1, Month 3, and Month 6
  - The mean change from Study Baseline and from Period 2 Baseline (as appropriate) for subjects with 1, 3, 6, 9, and 12 months exposure (revised per Amendment 06)
  - The mean change from Screening for the 1st 7 mornings and 2nd 7 mornings of the Follow-up Period
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period (revised per Amendment 02)
  - Change from Screening of sSOL on each of the 1st 3 nights, mean sSOL of the 1st 7 nights, and mean sSOL of the 2nd 7 nights of the Follow-up Period
  - Change from Screening of sWASO on each of the 1st 3 nights, mean sWASO of the 1st 7 nights and mean sWASO of the 2nd 7 nights of the Follow-up Period
  - Proportion of subjects whose sSOL is longer than at Screening for each of the 1st 3 nights, or whose mean sSOL is longer than at Screening for 1st 7 nights or 2nd 7 nights of the Follow-up Period
  - Proportion of subjects whose sWASO is higher than at Screening for each of the 1st 3 nights, or whose mean sWASO is higher than at Screening for the 1st 7 nights or 2nd 7 nights of the Follow-up Period

- Persistence of Effect
  - Mean change from Study Baseline of sSOL, of sSE, of sWASO and of sTST at Months 3, 6, 9, and 12 compared to Month 1
  - Mean change from Treatment Period 2 Baseline (Month 6) of sSOL, sSE, sWASO, and sTST at Months 9 and 12 compared to Month 7 (the first month of treatment in Period 2) (revised per Amendment 06)
  - Mean change from Study Baseline and Treatment Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO, and sTST at 3 and 6 months exposure compared to 1 month of exposure (revised per Amendment 06)

Safety and Tolerability of Lemborexant

- During Period 1, compared to PBO
- For subjects exposed to lemborexant for 3, 6, 9, and 12 months (revised per Amendment 06)

Exploratory Endpoints

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

- Change from Study Baseline in the mean value of the item on quality of sleep from the Sleep Diary for:
  - The 1st 7 mornings after the 1st dose in Period 1
  - Months 1, 3, and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in the mean value of the item on quality of sleep from the Sleep Diary for:
  - Subjects with 1, 3, 6, 9, and 12 months exposure (revised per Amendment 06)
- Change from Study Baseline in:
  - EQ-5D-3L at Months 1, 3, and 6
  - WPAI-GH at Months 3 and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in:
  - EQ-5D-3L for subjects with 3, 6, 9, and 12 months exposure (revised per Amendment 06)
  - WPAI-GH for subjects with 3, 6, 9, and 12 months exposure (revised per Amendment 06)
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item (1) at Months 1, 3, and 6 (placebo-controlled Treatment Period 1), and (2) with 3, 6, 9, and 12 months exposure (Treatment Period 1 and Treatment Period 2 combined). (revised per Amendment 06)
- Change from Study Baseline and Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO, sTST with 1, 3, 6, 9, and 12 months exposure, and ISI and FSS with 3, 6, 9, and 12 months exposure (revised per Amendment 06)
- Mean score on the T-BWSQ of LEM5, and LEM10 compared to PBO at End of Study
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10

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

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
- On-Treatment Safety Analysis Set: On-Treatment Safety Analysis Set is the group of subjects who received at least 1 dose of lemborexant and had at least 1 postdose safety assessment. (revised per Amendment 06)
- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement.
- On-Treatment Full Analysis Set (FAS): On-Treatment FAS is the group of subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement. (revised per Amendment 06)
- The Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan (SAP). (revised per Amendment 01)
- The 6-Months Completer Analysis Set is the group of subjects in the FAS who had all efficacy assessments up to and including Month 6 (ie, Week 1 and Months 1 to 6 visits) without missing primary or key secondary efficacy assessments at any of these visits. (revised per Amendment 04)
- The PK Analysis Set is the group of subjects who had at least 1 quantifiable lemborexant plasma concentration or its metabolites, with adequately documented dosing history.
- The PK/PD Analysis Set is the group of subjects receiving either lemborexant or PBO who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least 1 quantifiable lemborexant concentration data point as per the PK Analysis Set.

Efficacy Analyses

Definitions of Baseline

For the analyses of PBO-controlled endpoints (ie, Day 1 to Month 6), "Study Baseline" when applied to analysis endpoints is defined as the data captured during the Run-In Period (or during the Baseline Period). For the analyses of data that are not placebo-controlled (ie, Month 7 to Month 12), data from Month 6 will be used as the "Period 2 Baseline". (revised per Amendment 06)

For other endpoints, baseline data are captured during the Run-In and Baseline Period. Details will be specified in the SAP. (revised per Amendment 01)

12-Month Lemborexant Exposure

Twelve-month (12-month) lemborexant exposure summaries will be summarized by treatment (LEM5, LEM10) and duration of exposure (1 month [30 days] where appropriate, 3 months [90 days], 6 months [180 days], 9 months [270 days] and 12 months [365 days]). Treatment groups are LEM5 and LEM10, and include both (a) LEM Period 1 subjects on the On-Treatment Full Analysis Set using the change from Study Baseline and (b) LEM Period 2 subjects previously receiving PBO

on the On-Treatment Full Analysis Set using the change from Period 2 Baseline. (revised per Amendment 06)

Control of Type 1 Error

A sequential gate-keeping procedure including sSOL (primary endpoint), sSE and sWASO (key secondary endpoints) at Month 6 will control for type 1 error. In order to move from 1 step to the next (steps a to f; below) the outcome must be significant at 0.05 (2-sided).

a. Change from Study Baseline at Month 6 in sSOL, LEM10 compared to PBO
b. Change from Study Baseline at Month 6 in sSOL, LEM5 compared to PBO
c. Change from Study Baseline at Month 6 in sSE, LEM10 compared to PBO
d. Change from Study Baseline at Month 6 in sSE, LEM5 compared to PBO
e. Change from Study Baseline at Month 6 in sWASO, LEM10 compared to PBO
f. Change from Study Baseline at Month 6 in sWASO, LEM5 compared to PBO

This testing procedure controls the overall type 1 error rate of 0.05 for the primary and key secondary efficacy analyses. (revised per Amendment 03).

Analysis for the Primary Endpoint

Null Hypothesis: For sSOL, no difference exists in the mean change from Study Baseline to Month 6 of treatment with LEM10 and LEM5 as compared with PBO.

Alternative Hypothesis: For sSOL, a difference exists in the mean change from Study Baseline to Month 6 for LEM10 and LEM5 as compared with PBO.

The sSOL change from Study Baseline to Month 6 will be analyzed using the mixed effect model repeated measurement (MMRM) analysis on the FAS. The model will include all data and will be adjusted for the corresponding Study Baseline value, region, age group (<65 years old; ≥65 years old), treatment, time (average of the first 7 nights, Month 1, Month 3, and Month 6) and the interaction of treatment by time. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputations (MI) assuming the missing values are not missing at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed all primary efficacy assessments without missing values). (revised per Amendment 04) The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided. Details of the pattern mixture model and MI method will be presented in SAP. (revised per Amendments 03 and 04)

The following analyses will be considered as sensitivity analyses: (revised per Amendment 04)

- Missing imputation assuming MNAR utilizing CCMV-7: The same MMRM method used in the primary analysis will be applied utilizing CCMV-7 (ie, up to 7 monotone missing patterns will be used for missing value imputation). (revised per Amendment 04)
- Tipping point analysis: A range of shifts starting from the primary analysis (CCMV) will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to nonsignificant. (revised

per Amendment 04)

The following analyses will be considered as supplementary analyses (revised per Amendment 04):

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
- Completer analysis: The same primary efficacy analyses described above will be repeated based on 6-Months Completer Analysis Set (revised per Amendment 04).
- MMRM analysis assuming MAR: The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are missing at random (MAR). (revised per Amendment 03)

Key Secondary Efficacy and Pharmacodynamic Analyses (revised per Amendment 03)

The change from Study Baseline of key secondary endpoints sSE and sWASO at Month 6 comparing LEM5 and LEM10 to PBO will be analyzed using the same analysis method as the primary endpoint. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. The treatment comparison will be performed using contrasts. The p-value, LS means and the 95% confidence interval (CI) of the treatment differences will also be provided. (revised per Amendment 03)

Other Secondary Efficacy and Pharmacodynamic Analyses (revised per Amendment 03)

The other secondary efficacy endpoints (change from Study Baseline of the following for LEM5 and LEM10 compared to PBO; mean sSOL, mean sSE, mean sWASO and mean sTST at 1st 7 nights, Months 1 and 3; and mean sTST at Month 6; ISI total of 4 items of daytime functioning at Months 1, 3, and 6, and FSS score at Months 1, 3, and 6) will be analyzed using the MMRM, assuming the missing values are missing at random (MAR). The FSS will also be analyzed for responders, including only those subjects who endorsed clinically significant fatigue at Study Baseline. (revised per Amendments 03 and 06)

The proportion of responders, separately for sSOL and sWASO, will be analyzed using the Cochran-Mantel-Haenszel test, adjusted for country and age group, after the 1st 7 nights and for the last 7 nights of treatment at the end of Months 1, 3, 6, and 12, for LEM5 and LEM10 compared to PBO.

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

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

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for country, age group and treatment. The LS mean of each of the first 3 nights and each week of the Follow-up Period will be compared to the Screening Period between each treatment group and placebo. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper

bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen will be considered to evaluate whether clinically meaningful rebound insomnia is present.

To evaluate morning sleepiness item on the Sleep Diary, the mean change from Study Baseline of the 1st 7 mornings after the 1st dose in Period 1, Month 1, Month 3 and Month 6 will be analyzed using MMRM, assuming MAR. Additionally, morning sleepiness change from both Study Baseline and Period 2 Baseline for the 1st 7 mornings after the 1st dose in Period 2, Month 9, and Month 12, and also the change from Screening of each of the 2 weeks of the Follow-Up Period will be summarized with mean and 95% CI's. (revised per Amendment 03)

Analyses for persistence versus loss of effect will be conducted for sSOL, sSE, sWASO and sTST at Months 3, 6, 9, and 12 compared to Month 1. Loss of effect will be defined as present if the mean change from Study Baseline at Month 3 (or Months 6, 9, 12) is below the lower bound of the 95% CI at Month 1 for sSE or sTST and above the upper bound of the 95% CI at Month 1 for sSOL and sWASO. Analyses for persistence versus loss of effect over Period 2 will be conducted for only the subjects randomized to PBO in Period 1 (those subjects will have been randomized to lemborexant in Period 2). These analyses will compare sSOL, sSE, sWASO and sTST at Months 9 and 12 to these measures at Month 7. Loss of effect will be defined as present if the mean change from Period 2 Baseline at Month 9 (or Month 12) is below the lower bound of the 95% CI at Month 7 for sSE or sTST and above the upper bound of the 95% CI at Month 7 for sSOL and sWASO. Analyses for persistence versus loss of effect over duration of exposure will be conducted for On-Treatment Full Analysis Set subjects. These analyses will compare 1 month duration of exposure on sSOL, sSE, sWASO and sTST at 3 and 6 months duration of exposure, for a) LEM Period 1 subjects using the change from Study Baseline and (b) LEM Period 2 subjects previously receiving PBO using the change from Period 2 Baseline, with loss of effect as defined above. (revised per Amendment 06)

No multiplicity adjustment is planned for other secondary endpoints. (revised per Amendment 03)

Exploratory Efficacy and Pharmacodynamic Analyses

The change from Study Baseline for the mean score of the quality of sleep item on the Sleep Diary will be analyzed using MMRM, assuming MAR for the mean of the 1st 7 days of Period 1 and at Months 1, 3, and 6. (revised per Amendment 03)

Health-related quality of life: the change from Study Baseline for the EQ-5D-3L scores (both total score and Visual Analog Scale score), and the four scores from WPAI-GH will be using MMRM, assuming MAR for Month 1 (EQ-5D-3L only) and Months 3 and 6 (both EQ-5D-3L and WPAI-GH). (revised per Amendment 03)

Each item on the PGI-Insomnia at Months 1, 3 and 6 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

Summaries of all efficacy endpoints will be performed for 12 months exposure. Where appropriate, 95% CIs around the mean change from Study Baseline or Period 2 Baseline (for Period 1 and Period 2 data, respectively) will be presented. (revised per Amendment 06)

No multiplicity adjustment is planned for the exploratory and PD endpoints. (revised per Amendment 03)

Pharmacokinetic Analysis

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

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

Pharmacokinetic/Pharmacodynamic Analyses

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

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

Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set and On-Treatment Safety Analysis Set, as appropriate. The incidence of AEs, out-of-normal range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs and weight, suicidality (eC-SSRS), and T-BWSQ (including frequency and percentage of subjects with T-BWSQ ≥3), along with change from Study Baseline in laboratory safety test variables, ECGs, and vital sign and weight measurements, will be summarized by treatment group and visit using descriptive statistics. This will be repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and preferred terms related to drug abuse liability, will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. (revised per Amendment 03)

Other Analyses

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

Interim Analysis (revised per Amendments 04 and 05)

No interim analysis is planned for this study.

Sample Size Rationale

The sample size was estimated for the comparison of LEM10 and LEM5 with PBO, with respect to the mean change from Study Baseline at the end of Month 6 of the mean sSOL, mean sSE, and mean

sWASO. This estimate was based on sequential gate-keeping procedure at the 0.05 α-level as described above. There is sufficient power for both the primary endpoint (sSOL) and key secondary endpoints (sSE and sWASO).

On the basis of the dose finding study E2006-G000-201 (Study 201) for the lemborexant total summaries at Days 8 to 15, the standard deviation of change from Study Baseline for sSOL is assumed to be 33 minutes, for sSE is assumed to be 12% and for sWASO is assumed to be 43 minutes. The LS mean treatment differences at Days 8 to 15 from Study 201 were as follows: for sSE 9.5% for LEM10 and 5.5%, for LEM5; for sWASO -26.6 minutes for LEM10 and -11.3 minutes for LEM5. As a result of the non-normal distribution of sSOL, the LS mean treatment difference is not available (geometric mean ratios were used). Therefore, estimating treatment difference using medians at Days 8 to 15 from Study 201, leads to a median treatment difference of approximately -6.8 minutes for LEM10. For LEM5, a median treatment difference is approximately -13.2 minutes.

To detect a treatment difference in sSOL of at least -8.7 minutes, a sample size of 300 per treatment group at 5% (2-sided) level of significance has >90% power for comparing a dose of lemborexant with PBO.

To detect a treatment difference in sSE of at least 5.5%, a sample size of 300 per treatment group at 5% (2-sided) level of significance has >99% power for comparing a dose of lemborexant with PBO.

For sWASO, total 900 subjects (300 per treatment group) will give 90% power to detect a difference of -11.4 minutes for LEM5 and LEM10 compared to PBO. The study is adequately powered to show the statistically significant difference from PBO for LEM10 as well as for LEM5.

The study also has adequate power for the secondary analysis of responders. A sleep onset responder is defined as follows: sSOL at Study Baseline is ≥30 minutes and mean sSOL at 6 months is ≤20 minutes, and a sleep maintenance responder is defined as follows: sWASO at Study Baseline is ≥60 minutes and mean sWASO at 6 months ≤60 minutes and shows a reduction of >10 minutes compared to Study Baseline. A total of 900 subjects gives >99% power to detect a treatment difference in sleep onset responder rates of 16% and sleep maintenance responder rates of 24.4%.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
CCMV	complete case missing value
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CPAP	continuous positive airway pressure
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia—Suicide Severity Rating Scale
CV	curriculum vitae
CYP	Cytochrome P450
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic CRF
eC-SSRS	Columbia-Suicide Severity Scale, electronic version
EDC	electronic data capture
EDD	early drug discontinuation
EOS	end of study
EQ-5D-3L	EuroQOL version 5D-3L
ESS	Epworth Sleepiness Scale
ET	early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale

Abbreviation	Term
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSD-2	International Classification of Sleep Disorders, Version 2
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
IxRS	Interactive Randomization System
KSS	Karolinska Sleepiness Scale
LEM	lemborexant
LLN	lower limit of normal
LNH	low, normal, high
LPS	latency to persistent sleep
LS	least square
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MMRM	mixed effect model repeated measurement
M-MSLT	modified multiple sleep latency test
MNAR	missing not at random
OX1R	orexin-1 receptor
OX2R	orexin-2 receptor
PBO	placebo
PD	pharmacodynamic
PGI-Insomnia	Patient Global Impression - Insomnia
PI	Principal Investigator
PK	pharmacokinetic
PSG	polysomnography
QTc	Heart-rate-corrected QT interval
QTcB	QT interval corrected for Bazett's formula

Abbreviation	Term
QTcF	QT interval corrected for Fridericia's formula
RBC	red blood cell
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SDSB	Sleep Disorders Screening Battery
SMQ	standardized MedDRA query
SOC	system organ class
sSOL	subjective sleep onset latency
sSE	subjective sleep efficiency
sTST	subjective total sleep time
SUSAR	suspected unexpected serious adverse reaction
sWASO	subjective wake after sleep onset
T-BWSQ	Tyrer Benzodiazepine Withdrawal Symptom Questionnaire
TEAE	Treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WASO	wake after sleep onset
WBC	white blood cell
WHO-DD	World Health Organization – Drug Dictionary
WPAI-GH	Work Productivity and Activity Impairment Questionnaire – General Health

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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

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

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

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

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki

- ICH E6 Guideline for GCP of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP/ICH/135/95)
- Title 21 of the United States Code of Federal Regulations (US 21 Code of Federal Regulations [CFR]) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European Union member states
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or appropriate designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the risks and benefits involved, any discomfort, 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. Informed consent will be taken by personnel in accordance with national legislation. (revised per Amendment 01)

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

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

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

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 125 investigational sites in North America, South America, Europe, Asia, and Oceania. The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and the contract research organization(s) (CRO[s]) are listed in the Investigator Study File provided to each site. (revised per Amendment 03)

7 INTRODUCTION

7.1 Indication

Insomnia is a sleep disorder characterized by difficulties with sleep onset, sleep maintenance, or early morning awakening, in association with a complaint of impairment during the daytime. Insomnia is a widespread problem in industrialized nations, with approximately 30% of the population having symptoms and at least 6% of sufficient severity to merit treatment.

7.1.1 Current Therapeutic Options

Currently available pharmacological treatments used clinically for insomnia include benzodiazepines, non-benzodiazepine γ-aminobutyric acid (GABA) -releasing agents including $GABA_A$ receptor positive-allosteric modulators, antidepressants, melatonin and melatonin agonists, and antihistamines, and other prescription and nonprescription medications with sedative properties. Recently, there has been increased awareness of the need for sleep-promoting agents with new mechanisms of action.

Towards this end, research findings have suggested that central nervous system orexin receptors may be suitable targets for novel interventional strategies. This is supported by the recent approval of suvorexant, a drug in the same class as lemborexant which was shown in clinical trials to significantly improve sleep maintenance insomnia, but at the starting dose approved for use, showed suboptimal efficacy, particularly on sleep maintenance (Herring et al., 2016).

7.1.2 Lemborexant (E2006)

The generic name for E2006 has been designated as lemborexant.

7.1.2.1 Mechanism of Action

Orexin neuropeptides (orexin-A and orexin-B) have been recognized as critical upstream controllers of most wake-promoting neurotransmitters via 2 G-protein-coupled receptors, the orexin-1 receptor (OX1R) and the orexin-2 receptor (OX2R). On the basis of preclinical data, the OX2R has been speculated to be of greater importance for sleep/wake regulation than OX1R (Akanmu and Honda, 2005). Dual receptor antagonists are, however, more effective for sleep promotion than antagonists for either receptor alone (Moriarty et al., 2012). Lemborexant is a novel competitive dual orexin receptor antagonist, and therefore possesses a mechanism of action that may potentially be an effective treatment for insomnia disorder. This mechanism of action is the basis for the recent marketing approval of suvorexant, also an orexin receptor antagonist.

7.1.2.2 Clinical Experience with Lemborexant

7.1.2.2.1 PHASE 1

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

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

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

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

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

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

E2006-A001-008 (Study 008): food effect study. This study demonstrated a mild food effect. The C_{max} was decreased by 23% and $AUC_{(0\text{-inf})}$ was increased by 18% following consumption of a high fat meal.

E2006-A001-012 (Study 012): Drug-drug interaction study. This study demonstrated that: (1) coadministration of a moderate CYP3A inhibitor (fluconazole) led to a moderate

interaction as demonstrated by a 1.6-fold increase in C_{max} and 4.2-fold increase in $AUC_{0\text{-}inf}$ of lemborexant; (2) coadministration of lemborexant had no statistically significant effect on the PK of oral contraceptives (ethinyl estradiol and norethindrone), and these oral contraceptives did not alter the PK of lemborexant; and (3) coadministration of a gastric acid suppressant agent (famotidine) had a weak interaction with lemborexant as shown by a 27% decrease in C_{max} and no impact on $AUC_{0\text{-}inf}$ of lemborexant. (revised per Amendment 06)

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

7.1.2.2.2 PHASE 2

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

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

At doses up to 10 mg, changes from baseline in next-day sleepiness, as measured by the KSS, did not differ from those after placebo. At the highest doses of 15 and 25 mg, the increase in KSS from baseline was statistically significantly different from placebo at some time points, but the increases in KSS were of small magnitude (ie, less than 1 unit on average). Although there was approximately a 2-fold accumulation of lemborexant in plasma over the 15-day treatment period, next-day sleepiness did not increase from the beginning to the end of treatment.

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

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

Not applicable.

7.2 Study Rationale

Phase 1 and Phase 2 studies in the lemborexant clinical program have provided evidence for pharmacological efficacy at safe and well-tolerated doses (Section 7.1.2.2). The present study is designed to provide evidence from a large sample of subjects with insomnia disorder, that lemborexant is effective at doses that are safe and well tolerated and that do not cause meaningful morning sleepiness. This study will be part of the Phase 3 clinical study program, which is intended to support planned marketing applications.

Study 303 will also provide data on the safety of lemborexant over 12 months of treatment, in accordance with the ICH requirements for long-term administration. Study 303 will be conducted globally. The choice of countries will help ensure the enrollment of the requisite numbers of subjects from specific regions to facilitate the filing of regional Marketing Authorization Applications at the completion of the Phase 3 program.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is:

Determine the efficacy of lemborexant 5 mg (LEM5) and 10 mg (LEM10) compared to placebo (PBO) on subjective sleep onset latency (sSOL) after 6 months of treatment in subjects with insomnia disorder

8.2 Secondary Objective(s)

The key secondary objectives of the study are:

- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective sleep efficiency (sSE) after 6 months of treatment in subjects with insomnia disorder
- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective wake after sleep onset (sWASO) after 6 months of treatment in subjects with insomnia disorder

Additional secondary objectives of the study are:

- Determine the efficacy of LEM5 and LEM10 compared to PBO on sSOL, sSE, sWASO, and subjective total sleep time (sTST):
  - over the 1st 7 nights of treatment
  - after 1 month of treatment
  - after 3 months of treatment
- Determine the efficacy of LEM5 and LEM10 compared to PBO on sTST at 6 months
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to PBO as defined by response on sSOL or sWASO at 6 months and 12 months
- Evaluate the safety and tolerability of LEM5 and LEM10
- Evaluate the efficacy of LEM5 and LEM10 compared to PBO as measured by responses on the Insomnia Severity Index (ISI) and the Fatigue Severity Scale (FSS) after 6 months
- Evaluate rebound insomnia following discontinuation of treatment
- Evaluate morning sleepiness during and following completion of treatment
- Evaluate persistence of efficacy of LEM5 and LEM10 over 12 months

8.3 Exploratory Objective(s)

The following will be explored for both LEM5 and LEM10 compared to PBO over Treatment Period 1 (Period 1) and over Treatment Period 2 (Period 2) with analyses dependent on whether subjects received active treatment or PBO during Period 1 (revised per Amendment 04):

- Efficacy on quality of sleep
- Health outcomes on the EuroQOL version 5D-3L (EQ-5D-3L), Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH), and Patient Global Impression – Insomnia (PGI-Insomnia)
- Efficacy on sSOL, sSE, sWASO, sTST, ISI, and FSS
- Withdrawal symptoms after completion of treatment (Period 2 only)

The following will be explored for LEM5 and LEM10:

- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Population pharmacokinetic (PK) modeling for lemborexant
- PK/pharmacodynamic (PD) relationships between lemborexant concentrations and efficacy and safety variables

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 12-month, multicenter, randomized, controlled, double-blind, parallel-group study of 2 doses of lemborexant in approximately 900 male or female subjects with insomnia disorder (subjects who complain of difficulties with sleep onset and/or sleep maintenance). Approximately 40% of the population will be 65 years of age or older. Note: enrollment of subjects <65 years may be limited if the percentage of enrolled subjects ≥65 years is below expectations toward the end of the study. (revised per Amendments 01 and 03)

The study will have 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will comprise 3 periods and last up to 35 days: a Screening Period, a Run-In Period and a Baseline Period. The Randomization Phase will comprise a 6-month, placebo-controlled treatment period (Period 1). During the next 6 months (Period 2), subjects will receive only active treatment. Subjects will be informed that they will receive PBO at some point during the study and that all will receive active drug for at least 6 months. They will not be informed of either the timing of these periods or the timing of the 2nd randomization. A 2-week Follow-Up Period will then take place, followed by an End of Study Visit. (revised per Amendment 03)

End of Study

The end of the study will be the date of the last study visit for the last subject. As required by some regulatory agencies, the following estimates are provided:

- The study will begin enrollment in approximately November 2016 (revised per Amendments 01 and 03)
- The estimated duration for each subject on study is anticipated to be a maximum of60 weeks (a maximum 35-day Prerandomization Phase [that includes a Screening Period, a maximum 17-day Run-In Period, and a Baseline Period] + 52 weeks of the Randomization Phase + a 1-week window + a 2-week Follow-Up Period). (revised per Amendment 03)
- Approximately 900 subjects with insomnia disorder (18 years or older) will be randomized to receive LEM5 or LEM10 or PBO for 6 months. After 6 months, subjects who previously received lemborexant will continue to receive lemborexant at the same dosage level for an additional 6 months, while subjects who previously received PBO will undergo a 2nd randomization to receive LEM5 or LEM10 for 6 months.

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

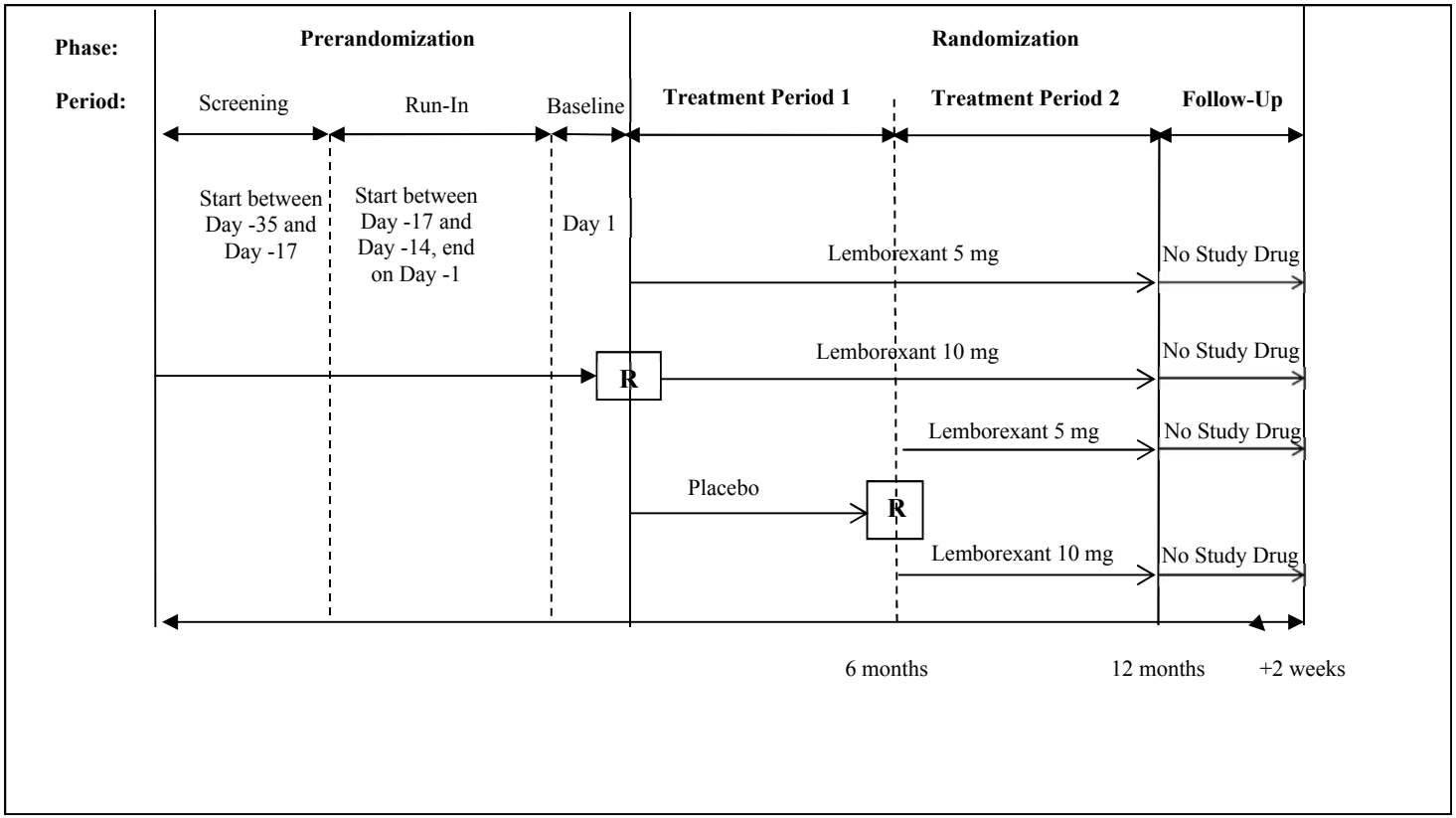

Figure 1 Study Design for Study E2006-G000-303 (revised per Amendment 03)

R = randomization

9.1.1 Prerandomization/Pretreatment Phase

9.1.1.1 Screening Period

The Screening Period will begin no more than 35 days before the subject is randomized. At the 1st screening visit (Visit 1), informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview will be conducted and will include confirmation that the subject meets diagnostic criteria for insomnia disorder, and further that the subject has a history of difficulties with sleep onset and/or sleep maintenance. Screening assessments will include the ISI, the Epworth Sleepiness Scale (ESS), the STOPBang, and the International Restless Legs Scale (IRLS), the latter 3 assessments collectively called the Sleep Disorders Screening Battery (SDSB). The FSS and health-related quality-of-life measures (EQ 5D-3L and WPAI-GH) will be administered. Safety assessments, including the electronic version of the Columbia-Suicide Severity Scale (eC-SSRS), will be conducted as described in Section 9.5.1.2. Additional eligibility criteria will be assessed (see Appendix 2). (revised per Amendment 03)

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

After subjects have completed the Sleep Diary on at least 7 consecutive mornings, provided that the Sleep Diary entries indicate continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, subjects will undergo the 2nd Screening Visit (Visit 2a). Subjects will return to the clinic and eligibility criteria will be determined. Subjects who are not eligible based on Sleep Diary entries will return to the clinic for debriefing purposes and to return study equipment. Visit 2a must occur between Day -17 and Day -14. A urine drug test will be performed. Subjects who continue to meet eligibility criteria will then receive PBO (single-blind) sufficient for 14 nights and will enter the Run-In Period which will last approximately 14 nights and a maximum of 17 nights. (revised per Amendment 03)

9.1.1.2 Run-In Period

The Run-in Period will begin once eligible subjects are dispensed PBO and will continue until the Baseline Period on Day 1. During the Run-in Period, subjects will take PBO each night immediately (ie, within 5 minutes) before bedtime (defined as the time the subject intends to try to fall asleep). They will be reminded that they must remain in bed for at least 7 hours each night and maintain a regular bedtime and time spent in bed trying to sleep throughout the study, according to the schedule determined by the study site and the subject.

They will also be reminded that they must follow study restrictions with regard to timing of meals, and use of caffeine and alcohol.

9.1.1.3 Baseline Period (Study Baseline)

On Day 1, the Run-in Period will end and the Baseline Period will begin. Subjects will return to the clinic for this visit (Visit 3), and the ISI will be administered. If subjects remain eligible, the FSS, EQ-5D-3L, and WPAI-GH will then be administered. Blood and urine samples will be collected for routine safety assessment, the eC-SSRS will be completed, and a urine drug test will be performed (Table 3). An electrocardiogram (ECG) will be performed, and vital signs and weight will be assessed. Subjects who complete the Baseline Period and continue to meet the eligibility criteria will be randomized and begin the Treatment Period.

9.1.2 Randomization Phase

Upon completion of baseline assessments on Day 1, subjects who remain eligible will enter the Randomization Phase. The purpose of the Randomization Phase will be (a) to assess the efficacy of lemborexant in subjects with insomnia disorder during treatment for at least 6 months, and (b) to assess long-term safety in subject treated with lemborexant for up to 12 months. The Randomization Phase will begin on Day 1 and will continue for 12 months.

A placebo-controlled treatment period (Period 1) will take place during the 1st 6 months of the Randomization Phase, immediately followed by a 2nd 6-month treatment period (Period 2), during which only active study drug will be administered. This will be immediately followed by a 2-week Follow-Up Period during which no study drug will be administered. At the start of Period 1, subjects will be randomized, in a double-blind manner, to receive LEM5 or LEM10, or PBO (approximately 1:1:1). Study drug will be dispensed and subjects will be provided with instructions to continue completing the Sleep Diary and taking study drug daily at home according to the same schedule and with the same restrictions as during the Run-in Period. At the start of Period 2, subjects who were randomized to receive PBO during Period 1 will be randomized, in a double-blind manner, to receive LEM5 or LEM10 (approximately 1:1).

All subjects will have routine safety monitored throughout the study, including treatment-emergent adverse events (TEAEs), 12-lead ECGs, vital signs, weight, and clinical hematology and blood chemistry labs. Suicidality will be assessed at Screening, Baseline, during the Randomization Phase, EOS and the ET/Early Drug Discontinuation (EDD) Visits, using the eC-SSRS.

9.1.2.1 Treatment Period 1 (Period 1)

Period 1 will begin with the 1st dose of randomized study medication. During Period 1, subjects will complete sleep diaries daily in the morning, within 1 hour of waketime; sleep diaries will be checked on a monthly basis. The subjects will return to the clinic for the Month 1, 2, 3, and 6 visits. In between these clinic visits, at the end of Months 4 and 5, study

site personnel will conduct a phone call to the subject to review any issues with completion of the Sleep Diary and to query concomitant medications and AEs. (revised per Amendment 03)

At the Month 1 visit, standard safety assessments will be conducted, a blood sample will be collected for determination of plasma concentrations of lemborexant and its metabolites, the ISI, the FSS, the PGI-Insomnia, the EQ-5D-3L, and the eC-SSRS will be completed, unused study drug will be collected, study drug compliance will be assessed, and a new supply of study drug will be dispensed (Section 9.4.8). At the Month 2 visit, standard safety assessments will be conducted. At the Month 3 visit, assessments will be same as those at the Month 1 visit, . At the end of Month 6, all assessments conducted at the Month 3 visit will be repeated, and the WPAI-GH will also be completed. At completion of these assessments, Period 1 will end and Period 2 will begin. For analysis purposes, a subject who completes assessments up to Month 6 will be defined as a Period 1 completer. (revised per Amendment 03)

9.1.2.2 Treatment Period 2 (Period 2)

At the end of Month 6 (Period 2 Baseline), subjects who received PBO during Period 1 will undergo a 2nd randomization to receive either LEM5 or LEM10 (approximately 1:1) during Period 2. Subjects who received lemborexant during Period 1 will continue to receive lemborexant at the same dose level during Period 2. Subjects will not be informed of the timing of the 2nd randomization (at the end of Month 6); allocation of dose will be double blind.

Subjects will continue to complete the Sleep Diary every morning. Sleep diaries will be checked on a monthly basis. The subjects will return to the clinic for the 9- and 12-month visits. In between these clinic visits, at the end of Months 7, 8, 10, and 11, study site personnel will conduct a phone call to the subject to review any issues with completion of the Sleep Diary and to query concomitant medications and AEs.

At each clinic visit, safety and tolerability will be assessed, the eC–SSRS will be completed, a urine drug test will be conducted, the Sleep Diary will be reviewed for completeness, compliance will be checked, and drug will be dispensed (except at the end of Month 12). At the end of Months 9 and 12, the ISI, FSS, the EQ-5D-3L, the PGI-Insomnia and the WPAI-GH will be completed. At predefined visits, a blood sample will be collected for PK analysis.

Period 2 will end with the completion of the 12-month visit. For analysis purposes, a subject who completes assessments through Period 2 will be defined as a study completer.

9.1.2.3 Follow-Up Period

The Follow-up Period will begin at the end of Period 2. Subjects will cease to take study drug but will continue to complete the Sleep Diary each morning until the End of Study visit.

9.1.2.4 End of Study Visit

At least 14 days but no more than 18 days after the Treatment Period, subjects will return to the clinic for the End of Study Visit.

At the End of Study Visit, in addition to standard safety assessments and the eC-SSRS, a urine drug test will be conducted, the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) will be administered and sleep diaries will be collected (Table 3). After the End of Study Visit, subjects' participation in the study will be finished.

9.1.2.5 Additional Study Information

The end of the study will be the date of the last study visit for the last subject. As required by some regulatory agencies, the following estimates are provided:

- The study will begin enrollment in approximately November 2016 (revised per Amendment 03)
- The estimated duration for each subject on study is anticipated to be a maximum of 60 weeks (a maximum 35-day Prerandomization Phase [that includes a Screening Period , a maximum 17-day Run-In Period, and a Baseline Period] + 52 weeks of the Randomization Phase + a 1-week window + a 2-week Follow-Up Period). (revised per Amendment 03)
- Approximately 900 subjects with insomnia disorder (18 years or older) will be randomized to receive LEM5 or LEM10 or PBO for 6 months. After 6 months, subjects who previously received lemborexant will continue to receive lemborexant at the same dosage level for an additional 6 months, while subjects who previously received PBO will undergo a 2nd randomization to receive LEM5 or LEM10 for 6 months.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Randomization

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce bias during data collection and evaluation of endpoints. In addition, in order to avoid bias, subjects will be informed only that all will receive PBO at some point in the study, and that all will receive active study drug for at least 6 months. They will not be informed that they will receive PBO during the run-in, and will not be informed of the timing of Periods 1 and 2, nor of the timing of the 2nd randomization (at the start of Period 2).

9.2.2 Run-In

Insomnia trials are associated with large placebo effects (McCall et al., 2003). This study will include a run-in period in which all subjects receive PBO (single-blind) to exclude subjects who no longer meet the study-specific criteria for insomnia disorder.

The Run-In Period will also help to identify and exclude subjects who are not compliant with the Sleep Diary instructions, duration of time spent in bed and/or restrictions on alcohol consumption before bedtime. In this regard, it is necessary for the subjects to be taking PBO and to obtain Sleep Diary data for approximately 14 nights to adequately evaluate whether they continue to meet the study-specific criteria for insomnia disorder and continue to comply with the study restrictions. (revised per Amendment 03)

9.2.3 Safety

To allow for a long-term safety evaluation, the present study will take place over a 12-month interval during which study drug will be taken daily by subjects, within 5 minutes before the subject intends to sleep.

To allow for correlation of plasma drug levels with safety, population PK-safety modelling will be conducted.

ADJUDICATION COMMITTEE (REVISED PER AMENDMENT 03)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [SMQ narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [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. (revised per Amendment 03)

DATA SAFETY MONITORING BOARD (REVISED PER AMENDMENT 03)

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination of whether the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 03)

9.2.4 Efficacy

To allow for evaluation of efficacy in insomnia disorder, this study will enroll only subjects who complain of difficulties with sleep onset and/or sleep maintenance. (revised per Amendment 03)

Subjective measures of sleep efficacy (sSOL and sWASO, derived from sleep diaries) will be the primary basis for assessment of efficacy on sleep. Study 201 showed that these measures yield results similar to those from objective PSG measurements. Sleep diary data provide information on the clinical impact of treatment from the subject's own perspective.

To allow for extensive assessments of efficacy, safety, and the impact of lemborexant treatment on insomnia disorder, a variety of other test instruments will also be employed. The ISI, which was also administered during Study 201, and the FSS will be administered. Other test instruments will be included to provide information on the functional consequences of insomnia disorder and on their possible improvement with treatment.

9.3 Selection of Study Population

Approximately 1500 subjects who have self-reported insomnia will be screened to provide 900 randomized subjects in North America, South America, Europe, Asia, and Oceania. 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, age 18 years or older at the time of informed consent

2. Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Insomnia Disorder, as follows:
   - Complains of dissatisfaction with nighttime sleep in the form of difficulty getting to sleep, difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment

3. At Screening: History of sSOL ≥30 minutes on at least 3 nights per week in the previous 4 weeks AND/OR sWASO ≥60 minutes on at least 3 nights per week in the previous 4 weeks (revised per Amendment 03)

4. At Screening: Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours

5. At 1st Screening Visit (Visit 1) and 2nd Screening Visit (Visit 2a): Reports regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00 (revised per Amendment 03)

6. At Screening and Study Baseline: ISI score ≥15

7. At the 2nd Screening Visit (Visit 2a): Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary completed on at least 7 consecutive mornings (minimum 5 of 7 for eligibility), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 03)

8. At the 2nd Screening Visit (Visit 2a): Confirmation of regular bedtimes and waketimes, as determined from responses on the Sleep Diary completed on a minimum of 7 consecutive mornings between the 1st and 2nd screening visit, such that the subject has a regular time spend in bed, either sleeping or trying to sleep, between 7 and 10 hours (revised per Amendment 03)

9. At the 2nd Screening Visit (Visit 2a): Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary completed on 7 mornings between the 1st and 2nd screening visit, such that there are not more than 2 nights with duration of time spent in bed <7 hours or >10 hours (revised per Amendment 03)

10. At Baseline (Visit 3a): Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary for the final 7 nights of the Run-in Period, such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights (revised per Amendment 03)

11. At Baseline (Visit 3a): Confirmation of regular bedtimes and waketimes such that the subject has a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours for the final 7 nights of the Run-In Period (revised per Amendment 03)

12. At Baseline (Visit 3a): Reconfirmation of regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject gets out of bed for the day, between 05:00 and 10:00, for the final 7 nights of the Run-In period (revised per Amendment 03)

13. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night (revised per Amendment 03)

14. Willing to not start a behavioral or other treatment program for 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 the study.

1. A current diagnosis of sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on the SDSB as follows:
   - STOPBang score ≥5
   - IRLS score ≥16
   - ESS score >15 (Scores of 11-15 require excessive daytime sleepiness must be recorded in subject's Medical History) (revised per Amendment 03)
2. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicate the need for referral for a diagnostic evaluation for the presence of narcolepsy
3. 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 asleep (revised per Amendment 03)
4. For subjects who underwent diagnostic PSG within 1 year before informed consent:
   - Age 18 to 64 years: Apnea-Hypopnea Index ≥10, or Periodic Limb Movements with Arousal Index ≥10
   - Age ≥65 years: Apnea-Hypopnea Index >15, or Periodic Limb Movements with Arousal Index >15
5. Beck Depression Inventory – II (BDI-II) score >19 at Screening
6. Beck Anxiety Inventory (BAI) score >15 at Screening
7. Habitually naps more than 3 times per week
8. Females who are breastfeeding or pregnant at Screening or Study Baseline (as documented by a positive serum beta-human chorionic gonadotropin [ß-hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
9. Females of childbearing who:
   - Had unprotected sexual intercourse within 30 days before study entry or who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, injectable contraceptives, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia)

throughout the entire study period or for 28 days after study drug discontinuation. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. (revised per Amendments 01, 02, and 03)

- Are currently abstinent, and do not agree to use a highly effective method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation. (revised per Amendment 02)
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation.

(NOTES: All females will be considered to be of childbearing 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].

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.) (revised per Amendment 02)

10. Excessive caffeine use that in the opinion of the investigator contributes to the subject's insomnia, or habitually consumes caffeine-containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study. Subjects are excluded if, in the previous 3 months, they had symptoms that would meet DSM-5 criteria for caffeine intoxication, which includes consumption of a high dose of caffeine (significantly in excess of 250 mg) and ≥5 of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of high energy, or psychomotor agitation. To be exclusionary, those symptoms must cause distress or impairment in social, occupational and other forms of functioning, and not be associated with other substance, mental disorder or medical condition. (revised per Amendment 01)

11. History of drug or alcohol dependency or abuse within approximately the previous 2 years

12. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to 2 or fewer drinks per day or forego alcohol within 3 hours before bedtime for the duration of his/her participation in the study

13. Known to be human immunodeficiency virus (HIV) positive

14. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening

15. A prolonged QT/QT interval corrected by Fridericia's formula (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms) (revised per Amendment 03)

16. Current evidence of clinically significant disease (eg, cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; severe hepatic insufficiency; gastrointestinal; renal including severe renal impairment; neurological [including subjects who lack capacity and/or whose cognitive decline indicates disorientation to person/place/time and/or situation] or psychiatric disease or malignancy within the past 5 years [other than adequately treated basal cell carcinoma]) or chronic pain that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments. Subjects for whom a sedating drug would be contraindicated for safety reasons because of the subject's occupation or activities are also excluded. (revised per Amendment 01)

17. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night

18. Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments

19. Any suicidal ideation with intent with or without a plan at Screening or Study Baseline or within 6 months of Study Baseline (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)

20. Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS) (revised per Amendment 03)

21. Scheduled for major surgery during the study (revised per Amendment 03)

22. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half lives, whichever is longer, before the 1st dose of study medication (Run-In Period). (A list of prohibited or limited concomitant medications is presented in Appendix 3.)

23. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half lives, whichever is longer, before the 1st dose of study medication (Run-In Period)

24. Failed treatment with suvorexant (efficacy or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator

25. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Study Baseline

26. A positive drug test at Screening, Run-In, or Baseline or unwilling to refrain from use of recreational drugs during the study (revised per Amendment 03)

27. Hypersensitivity to the study drug or any of the excipients

28. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5 times the half-life, whichever is longer preceding informed consent

29. 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. For subjects who discontinue study drug prematurely after randomization at Visit 3, the procedures are described in Section 9.5.5. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded.

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

LEM5, LEM10, or lemborexant-matched PBO taken orally in tablet form each night immediately before the time the subject intends to try to sleep

Run-In Period

- Days –17 and Day –1: PBO matched to lemborexant

Randomization Phase (Periods 1 and 2)

During Period 1 (Day 1 through end of Month 6), all subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized:

- LEM5: 1 lemborexant 5-mg tablet
- LEM10: 1 lemborexant 10-mg tablet
- PBO: 1 lemborexant-matched PBO tablet

During Period 2 (Month 7 through 12), all subjects will receive 1 tablet as described below, according to the treatment arm to which the subject has been randomized

- LEM5: 1 lemborexant 5-mg tablet
- LEM10: 1 lemborexant 10-mg tablet

9.4.2 Identity of Investigational Product(s)

Lemborexant (E2006) tablets and PBO to match lemborexant tablets will be manufactured by Eisai Manufacturing Ltd. and will be provided in strengths of 5 and 10 mg, identical in appearance. Tablets will be packaged in a double-blind manner. Each subject's treatment will be contained in a 17-day blister pack which includes 3 days overage (17 tablets) for the Run-In Period (Day -17 to -1), or a 1 month blister pack with 4 days overage (35 tablets) to allow for flexible visit scheduling.

A list of subjects receiving each study drug batch number will be provided in the study report.

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-fluoro pyridin-2-yl)cyclopropanecarboxamide
- Molecular formula: $C_{22}H_{20}F_2N_4O_2$
- Molecular weight: 410.42

9.4.2.2 Comparator Drug

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

9.4.2.3 Labeling for Study Drug

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

The following information has to be provided:

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

At Study Baseline (Day 1), subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The ratio of randomization to LEM5, LEM10, or to PBO, will be approximately 1:1:1, and stratified by country and age group (<65 years old; ≥65 years old). At the 2nd randomization, those previously randomized to PBO will be randomized to either LEM5 or LEM10 on an approximately 1:1 basis with the same stratification as in the 1st randomization. The randomization schemes and identification for each subject will be included in the final clinical study report for this study.

9.4.4 Selection of Doses in the Study

In Study 201, all doses studied met the 1st primary objective of balancing significant efficacy as measured by change from baseline in SE with sufficient safety measured by subjective sleepiness reported on the KSS. The 2nd primary objective was also achieved, as there were no significant increases in the KSS at 1 hour after waketime at the end of treatment. However, there were small dose-related increases in the KSS at both the beginning and end of treatment, and the rate of AEs of somnolence also increased with increasing dose level.

In Study 201, lemborexant 5 and 10 mg showed significant efficacy measured by sSE, as well as decreases in sSOL. These effects were maintained across the 15-day treatment period. For sleep maintenance, lemborexant 10 mg showed significant decreases, and while the magnitude of decreases in sWASO was less for 5 mg, there was a significant proportion of subjects whose sWASO decreased substantially, providing evidence for clinical benefit of 5 mg on sleep maintenance as well.

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

9.4.5 Selection and Timing of Dose for Each Subject

Throughout the Run-In Period and Treatment Periods 1 and 2, study drug will be taken at home immediately before the subject intends to sleep, on a time schedule that is as consistent as possible. Subjects should not eat a meal within 3 hours before taking the study drug. In addition to being a principle of good sleep hygiene, the rationale underlying this requirement is based on the mild food effect noted in Section 7.1.2.2.1. (revised per Amendment 01)

9.4.6 Blinding

During the Run-In Period, the subject will be blinded to the treatment, but study personnel will be aware that the treatment consists of PBO (ie, single-blind). Subjects will be informed that all will receive PBO at some point, and that all will receive active drug for at least 6 months. They will not be informed of either the timing of these periods or the timing of the 2nd randomization.

During Period 1 (ie, placebo-controlled, double-blind), subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff, will be blinded to the treatment codes (ie, double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedures. When all subjects have completed Period 1, all data will be unblinded to the sponsor. Study sites and subjects will remain blinded until the study has been completed (revised per Amendments 04 and 05)

A master list that identifies the treatment (ie, dose level) associated with each blister pack will be maintained in a sealed envelope to be stored in a secure area with limited access, by the clinical supply vendor, the vendor for the Interactive Randomization System (IxRS) and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior and Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the AE CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

9.4.7.1 Drug-Drug Interactions

Co-administration with strong and moderate 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 3. (revised per Amendment 06)

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications (Appendix 3) 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 1st dose of study medication (Run-In Period). (revised per Amendment 01)

Prohibited medications include strong and moderate CYP3A inhibitors and all CYP3A inducers. Prohibited therapies also include: any treatment for insomnia disorder, including any drugs or non-pharmacological treatment such as cognitive behavioral therapy; medications that are used for the purpose of inducing sleep (hypnotics) or inducing wakefulness (stimulants; except caffeine; see Section 9.4.7.2.1) and medications that have known sedating effects or alerting effects. This prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants). (revised per Amendment 06)

If a medication is not on the list of prohibited medications (Appendix 3) but in the opinion of the investigator causes or exacerbates the subject's insomnia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in Appendix 3, and if the investigator is uncertain whether the medication has known sedating or alerting effects, the Medical Monitor must be consulted. Note that strong and moderate CYP3A inhibitors and all CYP3A4 inducers will not be permitted at any time for any duration during the study. (revised per Amendment 06)

If a subject starts any prohibited medication or a new treatment/modality for insomnia disorder, 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. This provision continues to apply if a subject discontinues study medication but remains in the study (ie, continues to attend study visits and complete study assessments; see Section 9.5.5).

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.

9.4.7.2.1 Caffeine and Alcohol Restrictions

Caffeine will be permitted in limited quantities during the study. Subjects will be instructed to limit caffeine consumption to ≤4 cups of caffeinated beverages per day, or ≤400 mg

caffeine per day. Subjects will be instructed to avoid caffeine after 18:00 on all days during the study.

Alcohol will be permitted in limited quantities during the study. Subjects may consume a maximum of 2 alcohol-containing drinks on a given day while in the study, and will be instructed not to consume any alcohol within 3 hours before bedtime. Because the definition of a standard drink varies among countries and regions, no definition of the volume or alcohol content of a standard drink is provided, with the exception of Japan. For sites and subjects in Japan, a drink will be defined as 360 mL of beer, 150 mL of wine, or 50 mL of liquor. Compliance with these restrictions will be monitored by specific questions on the Sleep Diary. 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 blister packs returned to the investigator at the end of the Run-In and Treatment Periods.

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

At Study Baseline, if the subject continues to meet eligibility criteria but the treatment compliance check indicates that the subject has missed any doses of study medication, the investigator must use clinical judgment to decide if the subject should continue in the study.

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

9.4.9 Drug Supplies and Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572
- Financial Disclosure form(s) for the 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 trials agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

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

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

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor 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, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and together with unused study drugs that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demographic information will be collected at the Screening Visit. Demographic information will include birth year, sex, and race/ethnicity (where allowed). In applicable countries, to protect personal data, only the year of birth will be collected, and the month and date of each subject's date of birth will be masked where necessary as "January 1".

9.5.1.2 Screening and Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 5 years, except for history of any sleep disorder, which should be lifetime, must be noted in the Medical History and Current Medical Conditions CRF. If a subject has a score of 11-15 on the ESS at Screening, then the presence of excessive daytime sleepiness must be recorded in the subject's Medical History. Note that the presence of excessive daytime sleepiness in a subject's Medical History, combined with the definition of AE as specified in Section 9.5.1.5.1 means that only a worsening in daytime sleepiness during the study should be reported as an Adverse Event. Lifetime psychiatric history will also be obtained. A full physical examination will be performed, excluding a urogenital examination unless there are special circumstances and at the discretion of the investigator. The physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). The neurological examination must be conducted by a clinician whose clinical experience ensures that an adequate assessment of domains underlying the exclusion criteria can be performed. (revised per Amendments 01 and 03)

9.5.1.2.2 SLEEP DISORDERS HISTORY AND 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 SDSB will be administered (see below). (revised per Amendment 03)

The SDSB will include the following, to be self-administered by subjects: (revised per Amendment 03)

- The STOPBang: a list of 8 questions to be answered Yes or No, which screens subjects for obstructive sleep apnea (Chung et al., 2008)
- The IRLS: a subjective scale comprising 10 questions, which measures disease severity of restless legs syndrome (Abetz et al., 2006)
- The ESS: a questionnaire that rates the probability of falling asleep, on a scale of increasing probability from 0 to 3 for eight different situations that most people engage in during their daily lives, which assesses the severity of daytime sleepiness (Johns, 1992)

9.5.1.2.3 BECK DEPRESSION INVENTORY-II

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

9.5.1.2.4 BECK ANXIETY INVENTORY

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

9.5.1.2.5 VIRAL TESTING

At the Screening Visit, a 6-mL blood sample will be taken for detection of hepatitis B surface antigen and hepatitis C antibodies. (revised per Amendment 03)

9.5.1.3 Efficacy Assessments

9.5.1.3.1 ELECTRONIC SLEEP DIARY

An electronic sleep diary was developed for the purposes of the Phase 3 clinical program. Subjects must comply with requirements for completion of the sleep diary. Failure to comply will require discussion with the Medical Monitor and may result in discontinuation of the subject from the study.

The Sleep Diary will be completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-Up Period. This Sleep Diary will yield several self-reported measures of sleep that will be used to determine eligibility, as well as to assess efficacy. In addition, the Sleep Diary will include questions that relate to morning sleepiness and to alcohol consumption. (revised per Amendment 03)

SLEEP PARAMETERS

- sSOL: estimated minutes from the time the subject attempted to sleep until sleep onset

- sWASO: sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night
- sTST: derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
- sSE: proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reports attempting to sleep until the time the subject stopped trying to sleep for the night, and time spent asleep derived from time spent in bed minus sWASO (revised per Amendment 03)

QUALITY OF SLEEP AND MORNING SLEEPINESS

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

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

ALCOHOL CONSUMPTION

The Sleep Diary will include questions that ask about alcohol consumption the previous day, including within 3 hours before bedtime and/or exceeding the daily maximum of 2 alcoholic drinks per day.

9.5.1.3.2 INSOMNIA SEVERITY INDEX

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

9.5.1.3.3 FATIGUE SEVERITY SCALE (FSS)

The FSS is a self-report scale on which subjects are instructed to choose a number from 1 to 7 that indicates their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS score is the sum of all responses to the 9 questions (Krupp et al., 1989). Higher scores indicate greater fatigue.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples (4 mL per blood draw) will be obtained at prespecified visits for plasma concentrations of lemborexant and its metabolites M4, M9, and M10. When these blood

samples are obtained, the time of the 2 most recent doses administered before each sample will be documented. The handling and shipment of blood samples will be described in a manual to be provided to the study sites. Plasma concentrations of lemborexant and metabolites M4, M9, and M10 will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood for determination of plasma concentrations should also be drawn at the 1st report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.2 PHARMACODYNAMIC PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

PHARMACODYNAMIC ASSESSMENTS

There are no assessments that are primarily PD. For purposes of PK/PD modeling, selected efficacy and safety assessments will be used in lieu of PD assessments.

PHARMACOGENOMIC ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

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

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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(s) is lemborexant.

The criteria for identifying AEs in this study are:

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

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

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

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

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms 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. (revised per Amendment 03)

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 9.5.1.5.7 for a description of the eC-SSRS).

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

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

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

ASSESSING SEVERITY OF ADVERSE EVENTS

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the 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 AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 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 and AEs associated with study drug overdose, misuse, abuse, or medication error. These events with special situations are to be captured

using the SAE procedures but are to be considered as SAEs only if they meet 1 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 "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the 1st report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

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

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

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

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	alumin, calcium, cholesterol, globulin, glucose, iron, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

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

Table 2 Blood Sampling Schedule for All Laboratory and Pharmacokinetic Assessments

	Volume[a] per Sample Collection (mL)	Collection Time points	Total Volume[a] Collected (mL)
Clinical laboratory tests[b]	12	Screening Study Baseline Month 1 Month 3 Month 6 Month 9 Month 12 End of Study	96
Pregnancy testing	6	Screening	6
Viral tests	6	Screening	6
Pharmacokinetic sampling[b] (revised per Amendment 01)	4	Month 1 Month 3 Month 6 Month 9 Month 12	23
Total (revised per Amendment 01)			128 mL

a: Estimated volume.
b: Clinical laboratory tests and/or pharmacokinetic sampling will also be conducted at ET/EDD visits, and may also be obtained at unscheduled visits at the discretion of the investigator. (revised per Amendment 01)

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

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.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

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

measurements, and values will be recorded. Height (cm), and weight (kg) will also be measured.

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

9.5.1.5.5 PHYSICAL EXAMINATIONS

Physical examinations (full or brief) will be performed as designated on the Schedule of Procedures/Assessments (Table 3). At Screening and at the EOS/ET visit, a full physical examination will be conducted, including evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin. The full physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). A urogenital examination will only be required in the presence of clinical symptoms related to this region and at the discretion of the investigator. At other study visits as designated in Table 3, a brief physical examination will be conducted to assess health status by brief evaluation of the head, eyes, ears, nose, throat, heart, lungs, abdomen, and extremities, and other physical conditions of note. Documentation of the physical examinations, including the brief neurological examinations, will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

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

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

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

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

COLUMBIA-SUICIDE SEVERITY RATING SCALE

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

TYRER BENZODIAZEPINE WITHDRAWAL SYMPTOM QUESTIONNAIRE

An assessment of withdrawal symptoms will be made using the T-BWSQ completed at the EOS Visit. Subjects will be asked about the presence/absence and severity of the symptoms

listed in the questionnaire. For each listed symptom, the subject is to respond "No" (Score=0), "Yes – moderate" (Score=1) or "Yes – severe" (Score=2). The sum of responses will be the subject's score. (revised per Amendment 03)

PREGNANCY TESTS FOR WOMEN OF CHILD-BEARING

A serum β-hCG test will be performed at Screening for premenopausal women and postmenopausal women who have been amenorrheic for less than12 consecutive months. Subsequently, urine pregnancy tests will be conducted for these subjects as specified in the Schedule of Procedures/Assessments (Table 3).

9.5.1.6 Other Assessments

HEALTH-RELATED QUALITY OF LIFE ASSESSMENTS

EQ-5D-3L

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

PATIENT GLOBAL IMPRESSION – INSOMNIA

The PGI-Insomnia is a self-report assessment asking about subjects' perception of the effects of the study medication on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia does not have a baseline and the outcome is not change from baseline, but rather the global impression of the study medication's effects at the end of treatment. The PGI-Insomnia has 3 items related to study medication effects (a: helped/worsened sleep, b: decreased/increased time to fall asleep, and c: increased/decreased total sleep time) and 1 item related to perceived appropriateness of study medication strength. The 1st 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).

WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE – GENERAL HEALTH

The WPAI-GH collects data on absenteeism and presenteeism. The scale comprises 6 items that are used to create the 4 scores shown below. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

- Percent work time missed due to health
- Percent impairment while working due to health
- Percent overall work impairment due to health
- Percent activity impairment due to health

9.5.2 Schedule of Procedures/Assessments

Table 3 presents the Schedule of Procedures/Assessments for this study.

Table 3 Schedule of Procedures/Assessments

(revised per Amendments 01 and 03)

Phase	Prerandomization				Randomization															
Period	**Screening**		**Run-In[a]**	**Study Baseline**	**Treatment Period 1[a]**							**Treatment Period 2[a]**						**Follow-Up**		**ET/ EDD[b]**	**UNS[c]**
Visit[d]	**1**	**2a**	**2b**	**3a**	**3b**	**4[d]**	**5[d,]**	**6[d]**	**7[d,e]**	**8[d,e]**	**9[d]**	**10[d,e]**	**11[d,e]**	**12[d]**	**13[d,e]**	**14[d,e]**	**15[d]**		**EOS 16**		
Day	**–35 to –17**	**-17 to -14[f]**	**thru -1**	**1**																	
Month[g]	**–**	**–**				**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**(Wk 52 to 54)**	**(End Wk 54)**		
Procedures/ Assessments																					
Informed consent	X																				
Demographics	X																				
Inclusion/exclusion criteria[h]	X	X		X																	
Sleep Disorders Screening Battery[i]	X																				
Sleep, medical, and psychiatric history	X																				
Physical examination[j]	X			X		X	X	X			X			X			X		X	X	X
Height	X																				
Vital signs	X			X		X	X	X			X			X			X		X	X	X
Weight	X			X		X	X	X			X			X			X		X	X	
Insomnia Severity Index	X			X		X		X			X			X			X				
Fatigue Severity Scale	X			X		X		X			X			X			X				
Prior and concomitant medication(s)	←																				→
Beck Depression Inventory - II	X																				
Beck Anxiety Inventory	X																				
12-lead ECG[k]	X			X		X[l]		X[l]			X[l]			X[l]			X[l]		X[l]		
Urine pregnancy test[m]		X		X		X	X	X			X			X			X		X	X	
Serum pregnancy test (β-hCG)[m]	X																				
Urine drug test[n]	X	X		X		X	X	X			X			X			X		X	X[n]	X[n]
Serology (Hepatitis B and C)[o]	X																				
Clinical laboratory tests[p]	X			X		X		X			X			X			X		X	X	X
eC-SSRS	X			X		X		X			X			X			X		X	X	
Sleep diary[q]	←																				→
Dispense study drug			X		X	X	X	X			X			X							
Retrieve unused study drug				X		X	X	X			X			X			X				
Study drug compliance[r]				X		X	X	X			X			X			X				
Randomization					X[a,s]						X[a]										
EQ-5D-3L	X			X		X		X			X			X			X				
WPAI-GH	X			X				X			X			X			X				

Table 3 Schedule of Procedures/Assessments

(revised per Amendments 01 and 03)

Phase	Prerandomization				Randomization															
Period	**Screening**		**Run-In[a]**	**Study Baseline**	**Treatment Period 1[a]**							**Treatment Period 2[a]**						**Follow-Up**		**ET/ EDD[b]**	**UNS[c]**
Visit[d]	**1**	**2a**	**2b**	**3a**	**3b**	**4[d]**	**5[d,]**	**6[d]**	**7[d,e]**	**8[d,e]**	**9[d]**	**10[d,e]**	**11[d,e]**	**12[d]**	**13[d,e]**	**14[d,e]**	**15[d]**		**EOS 16**		
Day	**–35 to –17**	**-17 to -14[f]**	**thru -1**	**1**																	
Month[g]	**–**	**–**				**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**(Wk 52 to 54)**	**(End Wk 54)**		
Procedures/ Assessments																					
PGI-Insomnia						X		X			X			X			X				
T-BWSQ																			X		
Adverse events[t]	←																				→
Lemborexant PK sampling (plasma)[u]						X		X			X			X			X			X[v]	X

Footnotes for Table 3 (revised per Amendments 01 and 03)
AE = adverse event; ß-hCG = beta-human chorionic gonadotropin; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EDD = Early Drug Discontinuation; EOS = End of Study; EQ-5D-3L = EuroQOL version 5D-3L; ET = early termination; PGI-Insomnia = Patient Global Impression - Insomnia; PK = pharmacokinetics; T-BWSQ = Tyrer Benzodiazepine Withdrawal Symptom Questionnaire; UNS = unscheduled, WPAI-GH = Work Productivity and Activity Impairment Questionnaire – General Health.

a: Subjects will not be informed that placebo will be administered during the Run-In Period. They will also not be informed of the timing of the placebo-controlled period (Period 1) or the active-treatment (only) period (Period 2), and will not be informed of the timing of the 2nd randomization for subjects who received placebo during Period 1.

b: These assessments will be conducted at EOS, ET and EDD (except the T-BWSQ, which will not be conducted at EDD). Subjects who discontinue study drug prematurely at any time after randomization at Visit 3 (Study Baseline) will be encouraged to return to the site as soon as practicable (preferably within 7 days). These subjects will be encouraged to continue to complete all study assessments (excepting PK samples, which will not be taken), including the Sleep Diary, and to return for all subsequent clinic visits, without the administration of study medication. Subjects who do not agree to this will undergo an ET Visit and an EOS Visit. Subjects who do agree to continue with study procedures without the administration of study drug will undergo an EDD Visit. (revised per Amendment 01) These subjects need not attend the next regularly scheduled visit if this falls within the visit window of the next visit. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled visits.

c: Assessments during an UNS to be performed at the discretion of the investigator.

d: Visits 4, 5, and 6 are to be conducted within ±4 days of the schedule. Visits 7 through 15, and EOS to be done within ±7 days of the schedule. (revised per Amendments 01 and 03)

e: The site will telephone the subject to assess AEs, to record concomitant medications and to review the sleep diaries. If any AE is clinically significant and requires follow-up, a clinic visit should be arranged (Unscheduled Visit).

f: The Run-In Period may start between Day -17 and Day -14 and must continue for approximately 14 consecutive days and a maximum of 17 days. (revised per Amendment 01)

g: Defined as a calendar month.

h: Inclusion and exclusion criteria to be evaluated at visits other than or in addition to Visit 1 are listed in Appendix 2 (revised per Amendment 01).

i: Sleep Disorders Screening Battery comprises: STOPBang, International Restless Legs Scale, and Epworth Sleepiness Scale,. (revised per Amendments 01 and 03).

j: A full physical examination will be carried out at Screening and EOS (ET at the discretion of the investigator) and will include a brief neurological examination. A brief physical examination will be carried out at other visits.

k: The ECG should be repeated if an abnormality is observed .

l: If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as >450 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

m: Female subjects of child-bearing only.

n: Urine drug test to be conducted at Unscheduled Visits at the discretion of the investigator and at ET only for subjects who withdraw because of an Adverse Event.

o: Viral screening for hepatitis B (HBsAg) and hepatitis C (HCV antibody IgG) will be conducted.

p: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.

q: Subjects should complete the Sleep Diary, within 1 hour of waketime, each day throughout the study until EOS. Sleep diaries should be reviewed for eligibility: for the 7 consecutive days immediately before Visit 2, and for the Run-In Period at Visit 3. Thereafter, the Sleep Diary should be reviewed for completeness

once a month. (revised per Amendment 03)

r: Study drug compliance (tablet count) will be carried out at each clinic visit from Visit 3a through Visit 15. (revised per Amendments 01 and 03)

s: All other Baseline Period procedures must be completed and subject eligibility confirmed before randomization takes place and study drug is dispensed.

t: At each visit, subjects will be asked whether they have had a fall since the previous visit. If yes, supplemental information must be obtained to support a narrative for the event, per Section 9.2.3, Adjudication Committee. (revised per Amendment 03)

u: PK: A single blood sample (approximately 4 mL) for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be taken at each specified visit. The date and time of the 2 most recent doses administered before each sample will be documented.

v: PK sample will be collected at ET visit (not at EOS). (revised per Amendment 01)

9.5.3 Appropriateness of Measurements

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

The ISI has been widely used to evaluate the subjective impact of insomnia severity on psychosocial functioning, which is one type of daytime functioning impairment experienced by those with insomnia disorder. The FSS measures fatigue, which is another type of daytime impairment that is often a consequence of insomnia. This scale has been employed primarily in clinical trials of cognitive and behavioral treatments for insomnia disorder. Because the objectives of this study include assessing the response to lemborexant of both nighttime sleep and daytime impairment complaints, the ISI and the FSS will be evaluated for changes from baseline. The PGI-Insomnia, EQ-5D-3L and WPAI-GH will also be employed. These measures have been used in studies evaluating the impact of treatment for insomnia on patients' global perceptions of sleep quality and quality of life. Together these measures will provide a broad evaluation of the effects of lemborexant on each patient's sleep, daytime functioning, quality of life and productivity.

The safety assessments performed in this study, including clinical laboratory analyses, vital sign parameters, electrocardiograms, and assessment of AEs are standard evaluations to ensure subject safety. The C-SSRS, a standardized assessment required by regulatory authorities, will be used to evaluate any effects of lemborexant on suicidality. Additional safety-related assessments include evaluation of morning sleepiness and rebound insomnia, which will be measured using the validated Sleep Diary.

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

9.5.4.1 Reporting of Serious Adverse Events

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

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

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

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

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

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

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

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

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse 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 or as regionally required, the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

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

9.5.4.6 Regulatory Reporting of Adverse Events

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

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

9.5.5 Completion/Discontinuation of Subjects

For purposes of entering subject disposition in the eCRF, a subject will be considered to have completed the study per protocol after the End of Study visit has been completed. The subject may elect to discontinue the study at any time for any reason. Subjects who discontinue study drug prematurely at any time after randomization at Visit 3 (Study Baseline) will be encouraged to return to the site as soon as practicable (preferably within 7 days). These subjects will be encouraged to continue to complete all study assessments (excepting PK samples, which will not be taken), including the Sleep Diary, and to return for all subsequent clinic visits, without the administration of study medication.

Subjects who agree will undergo an EDD Visit, during which all assessments will be conducted that would be made at an ET visit (except the T-BWSQ). These subjects need not attend the next regularly scheduled visit if this falls within the visit window of the next visit. Subjects who discontinue early from study drug are considered on study as long as they return for their regularly scheduled visits.

Subjects who do not agree to this will undergo an ET Visit and an EOS Visit, as described in the Schedule of Procedures/Assessments (Table 3). (revised per Amendment 01)

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

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, lack of therapeutic effect, or administrative/other. Discontinuations due to noncompliance with alcohol restrictions will be assigned to “administrative/other”. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

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

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.4.3.1. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

Data required by the protocol will be collected in a validated data management system that is compliant with all regulatory requirements. These data include eCRFs, computer tablets and electronic sleep diaries. As defined by 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

Details of the statistical analyses will be included in a separate SAP. All statistical analyses will be performed by the sponsor or designee after the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required. (revised per Amendments 04 and 05)

9.7.1 Statistical and Analytical Plans

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

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

9.7.1.1 Study Endpoints

The following endpoints will be analyzed for LEM5 and LEM10 compared to PBO.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint will be the mean change from Study Baseline in sSOL at Month 6.

9.7.1.1.2 SECONDARY ENDPOINTS

The key secondary endpoints will be:

- Mean change from Study Baseline in sSE at Month 6
- Mean change from Study Baseline of sWASO at Month 6

Additional secondary endpoints will be:

- Mean change from Study Baseline of sSOL, of sSE, of sWASO and of sTST, at the beginning of treatment (mean of the 7 nights after the 1st dose in Period 1), at Month 1 and at Month 3
- Mean change from Study Baseline of sTST at Month 6
- Proportion of responders at Month 6 and Month 12, where sleep onset responder is defined as follows: sSOL at Study Baseline is ≥30 minutes and mean sSOL at 6 months is ≤20 minutes, and sleep maintenance responder is defined as follows: sWASO at Study Baseline is ≥60 minutes and mean sWASO at 6 months is ≤60 minutes and shows a reduction of >10 minutes compared to Study Baseline.
- Change from Study Baseline in daytime functioning, assessed as the total score from the 4 items on daytime functioning, on the ISI, at Months 1, 3, and 6
- Change from Study Baseline on the FSS at Months 1, 3, and 6
- Ratings on the morning sleepiness item of the Sleep Diary, for:
  - The mean change from Study Baseline of the 1st 7 mornings after the 1st dose in Period 1 and Period 2

- The mean change from Study Baseline at: Month 1, Month 3, and Month 6
- The mean change from Study Baseline and from Period 2 Baseline (as appropriate) for subjects with 1, 3, 6, 9 and 12 months exposure (revised per Amendment 06)
- The mean change from Screening for the 1st 7 mornings and 2nd 7 mornings of the Follow-up Period

- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period (revised per Amendment 02)
  - Change from Screening of sSOL on each of the 1st 3 nights, mean sSOL of the 1st 7 nights, and mean sSOL of the 2nd 7 nights of the Follow-up Period
  - Change from Screening of sWASO on each of the 1st 3 nights, mean sWASO of the 1st 7 nights and mean sWASO of the 2nd 7 nights of the Follow-up Period
  - Proportion of subjects whose sSOL is longer than at Screening for each of the 1st 3 nights, or whose mean sSOL is longer than at Screening for 1st 7 nights or 2nd 7 nights of the Follow-up Period
  - Proportion of subjects whose sWASO is higher than at Screening for each of the 1st 3 nights, or whose mean sWASO is higher than at Study Baseline for the 1st 7 nights or 2nd 7 nights of the Follow-up Period
- Persistence of Effect
  - Mean change from Study Baseline of sSOL, of sSE, of sWASO and of sTST at Months 3, 6, 9, and 12 compared to Month 1
  - Mean change from Period 2 Baseline (Month 6) of sSOL, of sSE, of sWASO and of sTST at Months 9 and 12 compared to Month 7 (the 1st month of treatment in Period 2)
  - Mean change from Study Baseline and Treatment Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO and sTST at 3 and 6 months exposure compared to 1 month of exposure (revised per Amendment 06)

9.7.1.1.3 SAFETY ENDPOINTS

Safety and Tolerability of Lemborexant

- During Period 1, compared to PBO
- For subjects exposed to lemborexant for 3, 6, 9, and 12 months (revised per Amendment 06)

9.7.1.1.4 EXPLORATORY ENDPOINTS

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

- Change from Study Baseline in the mean value of the item on quality of sleep from the Sleep Diary for:
  - The 1st 7 mornings after the 1st dose in Period 1

  - Months 1, 3, and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in the mean value of the item on quality of sleep from the Sleep Diary for:
  - Subjects with 1, 3, 6, 9, and 12 months exposure (revised per Amendment 06)
- Change from Study Baseline in:
  - EQ-5D-3L at Months 1, 3, and 6
  - WPAI-GH at Months 3 and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in:
  - EQ-5D-3L in subjects with 3, 6, 9, and 12 months exposure (revised per Amendment 06)
  - WPAI-GH in subjects with 3, 6, 9, and 12 months exposure (revised per Amendment 06)
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item (1) at Months 1, 3, and 6 (placebo-controlled Treatment Period 1), and (2) with 3, 6, 9, and 12 months exposure (Treatment Period 1 and Treatment Period 2 combined) (revised per Amendment 06)
- Change from Study Baseline and Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO, sTST with 1, 3, 6, 9, and 12 months exposure, and ISI and FSS with 3, 6, 9, and 12 months exposure. (revised per Amendment 06)
- Mean score on the T-BWSQ of LEM5, and LEM10 compared to PBO at End of Study
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- PK of lemborexant using population modeling
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

9.7.1.2 Definitions of Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
- On-Treatment Safety Analysis Set: On-Treatment Safety Analysis Set is the group of subjects who received at least 1 dose of lemborexant and had at least 1 postdose safety assessment (revised per Amendment 06)
- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement.
- On-Treatment Full Analysis Set (FAS): On-Treatment FAS is the group of subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement. (revised per Amendment 06)

- The Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the SAP.
- The 6-Months Completer Analysis Set is the group of subjects in the FAS who had all efficacy assessments up to and including Month 6 (ie, Week 1 and Months 1 to 6 visits) without missing primary or key secondary efficacy assessments at any of these visits. (revised per Amendment 04)
- The PK Analysis Set is the group of subjects who have at least 1 quantifiable lemborexant plasma concentration or its metabolites, with adequately documented dosing history.
- The PK/PD Analysis Set is the group of subjects receiving either lemborexant or PBO who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least 1 quantifiable lemborexant concentration data point as per the PK Analysis Set.

9.7.1.3 Subject Disposition

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

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

9.7.1.4 Demographic and Other Baseline Characteristics

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

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

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

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

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO-DDE/HD Mar 2014 or latest version). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO-DD preferred term (PT). (revised per Amendment 03)

Separate analyses will be provided for the Run-In Period, Treatment Period 1 and Treatment Period 2. (revised per Amendment 03)

For the Run-In Period, a prior medication is defined as a medication that stopped before the 1st dose of study medication in the Run-In Period. For Treatment Period 1, a prior medication is defined as a medication that stopped before the 1st dose of study medication in Treatment Period 1. For Treatment Period 2, a prior medication is defined as a medication that stopped before the 1st dose of study medication in Treatment Period 2. (revised per Amendment 03)

For the Run-In Period, a concomitant medication is defined as a medication that started on or before the 1st dose of study medication in the Run-In Period and continued during some or all of the Run-In Period. For Treatment Period 1, a concomitant medication is defined as a medication that started on or before the 1st dose of study medication in Treatment Period 1 and continued during some or all of that treatment period. For Treatment Period 2, a concomitant medication is defined as a medication that started on or before the 1st dose of study medication in Treatment Period 2. (revised per Amendment 03)

9.7.1.6 Efficacy Analyses

Where Sleep Diary endpoints are described, the time points refer to the mean of the final 7 nights before the visit unless otherwise stated.

Subjects who discontinue the treatment prematurely will be encouraged to continue to complete the assessments at the protocol defined times (retrieved drop out) until the scheduled time of termination. When available, these data will be used for efficacy analyses. If there are a substantial proportion of early withdrawals, a sensitivity analysis of the primary endpoint will be conducted.

<u>Definitions of Baseline</u>

For the analyses of PBO-controlled endpoints (ie, Day 1 to Month 6), "Study Baseline" is defined as the data captured during the Run-In Period (or during the Baseline Period). For the analyses of data that are not placebo-controlled (ie, Month 7 to Month 12), data from Month 6 visit will be used as the "Period 2 Baseline". (revised per Amendment 06)

For other endpoints, baseline data are captured during the Run-In and Baseline Period. Details will be specified in the SAP.

<u>12-Month Lemborexant Exposure</u>

Twelve-month (12-month) lemborexant exposure summaries will be summarized by treatment (LEM5, LEM10) and duration of exposure (1 month [30 days] where appropriate, 3 months [90 days], 6 months [180 days], 9 months [270 days] and 12 months [365 days]). Treatment groups are LEM5 and LEM10, and include both (a) LEM Period 1 subjects on the

On-Treatment Full Analysis Set using the change from Study Baseline and (b) LEM Period 2 subjects previously receiving PBO on the On-Treatment Full Analysis Set using the change from Period 2 Baseline. (revised per Amendment 06)

Control of Type 1 Error

A sequential gate-keeping procedure including sSOL (primary endpoint), sSE and sWASO (key secondary endpoints) at Month 6 will control for type 1 error. In order to move from 1 step to the next (steps a to f; below) the outcome must be significant at 0.05 (2-sided).

a. Change from Study Baseline at Month 6 in sSOL, LEM10 compared to PBO
b. Change from Study Baseline at Month 6 in sSOL, LEM5 compared to PBO
c. Change from Study Baseline at Month 6 in sSE, LEM10 compared to PBO
d. Change from Study Baseline at Month 6 in sSE, LEM5 compared to PBO
e. Change from Study Baseline at Month 6 in sWASO, LEM10 compared to PBO
f. Change from Study Baseline at Month 6 in sWASO, LEM5 compared to PBO

This testing procedure controls the overall type I error rate of 0.05 for the primary and key secondary efficacy analyses. (revised per Amendment 03).

9.7.1.6.1 ANALYSIS FOR THE PRIMARY ENDPOINT

Null Hypothesis: For sSOL, no difference exists in the mean change from Study Baseline to Month 6 of treatment with LEM10 and LEM5 as compared with PBO.

Alternative Hypothesis: For sSOL, a difference exists in the mean change from Study Baseline to Month 6 for LEM10 and LEM5 as compared with PBO.

The sSOL change from Study Baseline to Month 6 will be analyzed using the mixed effect model repeated measurement (MMRM) analysis on the FAS. The model will include all data and will be adjusted for the corresponding Study Baseline value, region, age group (<65 years old, ≥65 years old), treatment, time (average of the first 7 nights, Month 1, Month 3, and Month 6) and the interaction of treatment by time. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. The missing values will be imputed using a pattern mixture model utilizing multiple imputation (MI) assuming the missing values are missing not at random (MNAR) utilizing the complete case missing value pattern (CCMV - subjects who completed all primary efficacy assessments without missing values). (revised per Amendment 04) The missing values for a given visit will be imputed using all available values including the retrieved measurement from the post-discontinuation data. The treatment comparison will be performed using contrasts. The p-value, least square (LS) means and the 95% confidence interval (CI) for the treatment difference will also be provided. Details of pattern mixture model and MI method will be presented in SAP. (revised per Amendment 03)

The following analyses will be considered as sensitivity analyses (revised per Amendment 04):

- Missing imputation assuming MNAR utilizing CCMV-7: The same MMRM method used in the primary analysis will be applied utilizing CCMV-7 (ie, up to 7 monotone missing patterns will be used for missing value imputation). (revised per Amendment 04)
- Tipping point analysis: A range of shifts starting from the primary analysis (CCMV) will be used in the multiple imputation of missing data assuming MNAR to identify the specific shift and treatment effect that will tip the results from statistically significant to non-significant. (revised per Amendment 04)

The following analyses will be considered as supplementary analyses (revised per Amendment 04):

- PP analysis: The same primary efficacy analyses described above will be repeated based on PP analysis set.
    - Completer analysis: The same primary efficacy analyses described above will be repeated based on 6-Months Completer Analysis Set. (revised per Amendment 04).
- MMRM analysis assuming MAR: The same primary endpoint analysis described above will be analyzed using MMRM assuming the missing values are missing at random (MAR). (revised per Amendment 03)

9.7.1.6.2 SECONDARY EFFICACY AND PHARMACODYNAMIC ANALYSES

Key Secondary Efficacy Analyses (revised per Amendment 03)

The change from Study Baseline of key secondary endpoints sSE and sWASO at Month 6 comparing LEM5 and LEM10 to PBO will be analyzed using the same analysis method as the primary endpoint. The missing values will be imputed using a pattern mixture model utilizing MI assuming MNAR. The treatment comparison will be performed using contrasts. The p-value, LS means and the 95% confidence interval (CI) of the treatment differences will also be provided. (revised per Amendment 03)

Other Secondary Efficacy Analyses (revised per Amendment 03)

The other secondary efficacy endpoints (change from Study Baseline of the following for LEM5 and LEM10 compared to PBO; mean sSOL, mean sSE, mean sWASO and mean sTST at 1st 7 nights, Months 1 and 3; and mean sTST at Month 6; ISI total of 4 items of daytime functioning at Months 1, 3, and 6, and FSS score at Months 1, 3, and 6) will be analyzed using MMRM, assuming MAR. The FSS will also be analyzed for responders, including only those subjects who endorsed clinically significant fatigue at Study Baseline. (revised per Amendments 03 and 06)

The proportion of responders, separately for sSOL and sWASO, will be analyzed using the Cochran-Mantel-Haenszel test, adjusted for country and age group, after the 1st 7 nights and for the last 7 nights of treatment at the end of Months 1, 3, 6 and 12, for LEM5 and LEM10 compared to PBO.

Rebound insomnia is defined as worsened sleep relative to Screening after study drug treatment is completed. Sleep Diary data from the Follow-up Period will be compared to Sleep Diary data from the Screening Period to assess whether subjects experience rebound

insomnia. Specifically, a higher value for sSOL or sWASO during the Follow-up Period compared to the mean sSOL or sWASO value during the Screening Period will be considered worsened sleep.

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

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for country, age group and treatment. The LS mean of each of the first 3 nights and each week of the Follow-up Period will be compared to the Screening Period between each treatment group and placebo. If the lower bound of the 95% CI of sSOL or sWASO for each of the first 3 nights and the mean of each week of the Follow-Up Period exceeds the upper bound of a 95% CI for the values during the Screening Period in the given treatment group, it will be considered strong evidence for rebound insomnia. If the LS means for sSOL and sWASO for the Follow-up Period are all lower than for the Screening Period, then no rebound insomnia is suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen will be considered to evaluate whether clinically meaningful rebound insomnia is present.

To evaluate morning sleepiness item on the Sleep Diary, the mean change from Study Baseline of the 1st 7 mornings after the 1st dose in Period 1, Month 1, Month 3 and Month 6 will be analyzed using MMRM, assuming MAR. Additionally, morning sleepiness change from both Study Baseline and Period 2 Baseline for the 1st 7 mornings after the 1st dose in Period 2, Month 9, and Month 12, and also the change from Screening of each of the 2 weeks of the Follow-Up Period will be summarized with mean and 95% CI's. (revised per Amendment 03)

Analyses for persistence versus loss of effect will be conducted for sSOL, sSE, sWASO and sTST at Months 3, 6, 9, and 12 compared to Month 1. Loss of effect will be defined as present if the mean change from Study Baseline at Month 3 (or Months 6, 9, 12) is below the lower bound of the 95% CI at Month 1 for sSE or sTST and above the upper bound of the 95% CI at Month 1 for sSOL and sWASO. Analyses for persistence versus loss of effect over Period 2 will be conducted for only the subjects randomized to PBO in Period 1 (those subjects will have been randomized to lemborexant in Period 2). These analyses will compare sSOL, sSE, sWASO and sTST at Months 9 and 12 to these measures at Month 7. Loss of effect will be defined as present if the mean change from Period 2 Baseline at Month 9 (or Month 12) is below the lower bound of the 95% CI at Month 7 for sSE or sTST and above the upper bound of the 95% CI at Month 7 for sSOL and sWASO. Analyses for persistence versus loss of effect over duration of exposure will be conducted for On-Treatment Full Analysis Set subjects. These analyses will compare 1 month duration of exposure on sSOL, sSE, sWASO and sTST at 3 and 6 months duration of exposure, for (a) LEM Period 1 subjects using the change from Study Baseline and (b) LEM Period 2 subjects

previously receiving PBO using the change from Period 2 Baseline, with loss of effect as defined above. (revised per Amendment 06)

No multiplicity adjustment is planned for other secondary endpoints. (revised per Amendment 03)

9.7.1.6.3 EXPLORATORY EFFICACY AND PHARMACODYNAMIC ANALYSES

The change from Study Baseline for the mean score of the quality of sleep item on the Sleep Diary will be analyzed using MMRM, assuming MAR for the mean of the 1st 7 days of Period 1 and at Months 1, 3, and 6. (revised per Amendment 03)

Health-related quality of life: the change from Study Baseline for the EQ-5D-3L scores (both total score and Visual Analog Scale score), and the four scores from WPAI-GH will be using MMRM, assuming MAR for Month 1 (EQ-5D-3L only) and Months 3 and 6 (both EQ-5D-3L and WPAI-GH). (revised per Amendment 03)

Each item on the PGI-Insomnia at Months 1, 3, and 6 will be analyzed separately by calculating the number and percentages of subjects for each response category (eg, negative [3], neutral [2], positive [1] medication effect). The percentage of positive responses will be compared between treatment groups using the chi-square test, and repeated for age subgroups.

Summaries of all efficacy endpoints will be performed for 12 months exposure. Where appropriate, 95% CIs around the mean change from Study Baseline or Period 2 Baseline (for Period 1 and Period 2 data, respectively) will be presented. (revised per Amendment 06)

No multiplicity adjustment is planned for the exploratory and pharmacodynamic endpoints. (revised per Amendment 03)

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

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

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

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

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

9.7.1.7.3 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The PK/PD relationship between exposure to lemborexant and the efficacy variables including but not limited to sSOL, sSE, and sWASO, and the safety variables including but not limited to morning sleepiness and frequently occurring TEAEs, will be explored graphically. Any emergent PK/PD relationships will be evaluated by population PK/PD modeling. The population PK/PD analysis plan will be described and results will be reported in a separate document.

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

9.7.1.7.4 PHARMACOGENOMIC ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set and On-Treatment Safety Analysis Set, as appropriate. (revised per Amendment 06)

12-Month Lemborexant Exposure

For visit-based Safety data (ie, laboratory values, vital signs, ECGs, etc), data will be summarized by treatment (LEM5, LEM10) and duration of exposure (1 month, 3 months, 6 months, 9 months, and 12 months). Treatment groups are LEM5 and LEM10, and include both (a) LEM Period 1 subjects on the On-Treatment Safety Analysis Set using the change from Study Baseline, and (b) LEM Period 2 subjects previously receiving PBO on the On-Treatment Safety Analysis Set using the change from Period 2 Baseline. (revised per Amendment 06)

Summaries of exposure and AEs will be summarized for:

- Period 1 data, where treatment groups are PBO, LEM5 and LEM10 on the Safety Analysis Set
- 12-month LEM exposure, where treatment groups are LEM5 and LEM10, and include both (a) LEM Period 1 subjects on the On-Treatment Safety Analysis Set, and (b) LEM Period 2 subjects previously receiving PBO on the On-Treatment Safety Analysis Set. (revised per Amendment 06)

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. Period 1 data with LEM5 or LEM10 will be summarized for: the number (percent) of subjects who completed 1 month (30 or more days), 3 months (90 or more days), and 6 months (180 or more days). Twelve-month (12-month) exposure with LEM5 or LEM10 will be summarized for: the number (percent) of subjects who completed 3 months (90 or more days), 6 months (180 or more days), 9 months (270 days), and 12 months (365 or more days) of dosing. (revised per Amendment 06)

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

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 17.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

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

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

Separately, for 12-month exposure analysis, LEM Period 2 subjects previously receiving PBO on the On-Treatment Safety Analysis Set will have a separate definition for TEAE in Period 2, where an AE is defined as (revised per Amendment 06):

- Emerges during Period 2 having been absent prior to Period 2 treatment, or
- Reemerges during treatment, having been present prior to Period 2 treatment but stopped before Period 2 treatment, or
- Worsens in severity during Period 2 treatment relative to the pre Period 2 state, when the AE is continuous.

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

Adverse events will be summarized using the Safety Analysis Set and, where appropriate, the On-Treatment Safety Analysis Set. The TEAEs will be summarized by treatment group at the start of the TEAE. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs during the Run-In Period, and after the Run-In Period will be summarized separately. The number (percentage) of subjects with TEAEs during the Period 1 (Safety Analysis Set) and 12-month LEM exposure (On-Treatment Safety Analysis Set) will also be summarized separately. (revised per Amendment 06)

All the following summaries will be repeated for Period 1 and 12-month LEM exposure. (revised per Amendment 06)

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

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

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

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

The number (percentage) of subjects with TEAEs of cataplexy or other events that are characterized according to the customized MedDRA query PT as cataplexy-related events, as well as somnolence and related events, and drug abuse liability will be summarized separately. The number of adjudicated events based on the report of the Adjudication Committee will also reported separately.

Customized MedDRA Queries (CMQ) for AEs that could potentially be considered cataplexy or seizure, somnolence, and related events, and preferred terms related to drug abuse liability, will be summarized. The results of the deliberation of the Adjudication Committee will be reported separately. (revised per Amendment 03)

9.7.1.8.3 LABORATORY VALUES

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this study. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum for continuous variables, and number and percentage for categorical variables) for the laboratory parameters and changes from Study Baseline will be evaluated by treatment group and visit. This will also be repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

Laboratory test results will be assigned a low, normal, high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the Study Baseline LNH classification to the LNH classification at Month 6 by treatment group. This will also be repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

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

9.7.1.8.4 VITAL SIGNS AND WEIGHT

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

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range. Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented for change from Study Baseline (Safety Analysis Set), by treatment group and by time point. This will also be repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

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

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

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from Study Baseline (Safety Analysis Set) will be presented by treatment group and visit. This will also be repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

Shift tables will present changes from Study Baseline in ECG interpretation (categorized as normal and abnormal) by time point. (revised per Amendment 03)

For each subject, the maximum observed QTcF, the corrected QT interval calculated using Bazett's formula (QTcB), and the maximum prolongation from Study Baseline in QTcF will be compiled. Categorical analyses of subjects (number and percent) with maximum observed QTcF values >450 ms, >480 ms, and >500 ms and maximum prolongations (from Study Baseline) in QTcF >30 ms and >60 ms will be presented by treatment group and by time point. Categorical analyses of subjects (number and percent) with maximum observed PR values >220 ms, and QRS values >120 ms will be presented by treatment group and by time point. This will also be repeated for the 12-month LEM exposure (On-Treatment Safety

Analysis Set), summarized by treatment group and duration of exposure. (revised per Amendment 06)

9.7.1.8.6 OTHER SAFETY ANALYSES

The results of eC-SSRS assessments will be listed for each subject. The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group as appropriate. Urine drug test results and pregnancy test results will also be listed.

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

9.7.1.9 Other Analyses

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

9.7.2 Determination of Sample Size

The sample size was estimated for the comparison of LEM10 and LEM5 with PBO, with respect to the mean change from Study Baseline at the end of Month 6 of the mean sSOL, the mean sSE and mean sWASO. This estimate was based on sequential gate-keeping procedure at the 0.05 α-level as described above. There is sufficient power for both the primary endpoint (sSOL) and key secondary endpoints (sSE and sWASO).

On the basis of the dose finding study E2006-G000-201 (Study 201) for the lemborexant total summaries at Days 8 to 15, the standard deviation of change from Study Baseline for sSOL is assumed to be 33 minutes, for sSE is assumed to be 12% and for sWASO is assumed to be 43 minutes. The LS mean treatment differences at Days 8 to 15 from Study 201 were as follows: for sSE 9.5% for LEM10 and 5.5%, for LEM5; for sWASO -26.6 minutes for LEM10, and -11.3 minutes for LEM5. As a result of the non-normal distribution of sSOL, the LS mean treatment difference is not available (geometric mean ratios were used). Therefore, estimating treatment difference using medians at Days 8 to 15 from Study 201, leads to a median treatment difference of approximately -6.8 minutes for LEM10. For LEM5, a median treatment difference is approximately -13.2 minutes.

To detect a treatment difference in sSOL of at least -8.7 minutes, a sample size of 300 per treatment group at 5% (2-sided) level of significance has >90% power for comparing a dose of lemborexant with PBO.

To detect a treatment difference in sSE of at least 5.5%, a sample size of 300 per treatment group at 5% (2-sided) level of significance has >99% power for comparing a dose of lemborexant with PBO.

For sWASO, total 900 subjects (300 per treatment group) will give 90% power to detect a difference of -11.4 minutes for LEM5 and LEM10 compared to PBO (Table 4). The study is adequately powered to show the statistically significant difference from PBO for LEM10 as well as for LEM5.

Table 4 Sample Size Calculations for Study E2006-G000-303

Alpha=0.05	Difference between Active and Placebo CfB (min)	Power = 80%		Power =90%	
		Sample size per group	Overall 3 group sample size	Sample size per group	Overall 3 group sample size
sSOL (SD=33)	-6.8	371	1113	496	1488
	-7.6	300	900	398	1194
	-8	269	807	359	1077
	-8.7	229	687	**300**	**900**
	-9	213	639	284	852
	-10	172	516	230	690
	-11	143	429	191	573
sWASO (SD=43)	-9	360	1080	481	1443
	-9.9	300	900	398	1194
	-10	292	876	390	1170
	-11	241	723	323	969
	-11.4	225	675	**300**	**900**
	-12	203	609	271	813

CfB = change from baseline, sSOL = subjective sleep onset latency, sWASO = subjective wake after sleep onset.

The study also has adequate power for the secondary analysis of responders. A sleep onset responder is defined as follows: sSOL at Study Baseline is ≥30 minutes and mean sSOL at 6 months is ≤20 minutes, and a sleep maintenance responder is defined as follows: sWASO at Study Baseline is ≥60 minutes and mean sWASO at 6 months is ≤60 minutes and shows a reduction of >10 minutes compared to Study Baseline. A total of 900 subjects gives >99% power to detect a treatment difference in sleep onset responder rates of 16% and sleep maintenance responder rates of 24.4%.

The above sample size also meets regulatory safety requirements. Even with early discontinuation rates as high as 50% at Month 6 (ie, 150 subjects remaining) and 60% by Month 12 (ie, 120 subjects remaining in each treatment group), the requirement for 100 subjects in each of the elderly and non-elderly age-groups to complete 12-months of treatment on 5 or 10 mg lemborexant will be met. In addition, 420 total subjects would have completed 6 months of treatment of 5 mg or 10 mg lemborexant.

9.7.3 Interim Analysis

No interim analysis is planned for this study. (revised per Amendments 04 and 05)

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 or appropriate study team member and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

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

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The 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 GCP and local regulations. All records at the site are subject to inspection by the appropriate Regulatory Authorities and to IRB/IEC review.

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

- Subject clinical records
- Copies or transcribed health care provider notes that have been certified for accuracy after production

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

11.4 Recording of Data

Data entered into the electronic data capture (EDC) system must be accurate and complete. Responsible site personnel will enter the data required by the protocol in the eCRFs in accordance with the eCRF Completion Guidelines provided by the Sponsor. All the eCRF data collected in the EDC system will be archived in CDs and will be forwarded to the Sponsor at the end of the study.

- All corrections made to data entered in the eCRFs will require a reason for change
- The Principal Investigator will review all eCRF data entered in the EDC system and will electronically sign off to attest to the review
- Data reported on the eCRF that are derived from source documents should be consistent with the source documents, and if not, the discrepancy should be explained
- The Principal Investigator will use a subject identification number to identify subjects in the study

Data corrections made to eCRF data entered in the EDC system will be verified by CRA personnel using source documents.

The expectation for timely completion of eCRFs can be found in the eCRF Completion Guidelines. All sites should complete data entry for all visits in accordance with these Guidelines. Entry of all data from the Month 6 visit, and all corresponding data, must in no case be completed later than 2 weeks after the Month 6 visit.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. The investigator agrees to allow direct access to source documents and study facilities to sponsor

representative(s), monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. (revised per Amendment 01)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence) and subject source data. In addition, upon request, 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 standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

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

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

11.9 Publication of Results

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

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

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

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

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

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

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance in accordance with local guidelines and requirements for subject participation in this study.

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	Fasting glucose value: >160 – 250 mg/dL	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L;	>500 mg/dL; >27.8 mmol/L;

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	>ULN – 8.9 mmol/L	>8.9 – 13.9 mmol/L	hospitalization indicated	life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: 28 May 2009 (v4.03: 14 Jun 2010).

Appendix 2 Inclusion/Exclusion Criteria Schedule

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

(revised per Amendment 02)

Visit Name	V1	V2a	V3a
	Screening	Screening	Screening/ Baseline 1
Inclusion Criterion Number	1, 2, 3, 4, 5, 6, 13, 14	7, 8, 9	6, 10, 11, 12, 13, 14
Exclusion Criterion Number	1 – 29	8, 22, 23,26	8, 15, 17, 19, 21, 25, 26

Appendix 3 Prohibited Concomitant Medications

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

Category	Medication
Anticholinergics (centrally-acting)	-
Anticonvulsants with known sedating effects	Barbiturates Benzodiazepines GABA analogues Hydantoins Phenyltriazines
Antihistamines (centrally-acting H1, including over the counter) (revised per Amendment 03)	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 (revised per Amendments 01 and 03)	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

Category	Medication
Moderate CYP3A inhibitors (revised per Amendment 06)	Amprenavir Aprepitant Atazanavir Casopitant Cimetidine Ciprofloxacin Clotrimazole Crizotinib Cyclosporin Darunavir Dronadarone Erythromycin Faldaprevir Fluconazole Fluvoxamine Imatinib Netupitant Tofisopam Verapamil
CYP3A inducers (revised per Amendments 01 and 03)	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	-
MAOIs	-
Opioid Analgesics	-

Category	Medication
Muscle relaxants (centrally-acting) with known sedating effects	GABA analogues Hydantoins Phenyltriazines
Stimulants	Amphetamines Modafinil Armodafinil Methylfenidate
Other	Warfarin, heparin, ticlopidine Non-stimulant diet pills Systemic isoretinoin Systemic glucocorticoids Tryptophan

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-G000-303

Study Protocol Title: A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel-Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder

Investigational Product Name: E2006/lemborexant

IND Number: 111871

EudraCT Number: 2015-001463-39

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