Revision History
Previous Version: v9.0
Current Version: v10.0
Date of Latest Revision: 20 June 2018 (revised per Amendment 06)

Change	Rationale	Affected Protocol Section(s)
Revised objectives	To reflect exploratory nature of this Phase 2 study	• Synopsis: • Objectives • Section 8
Updated Adjudication Committee information	To harmonize with other protocols in the lemborexant clinical program	• Synopsis • Adjudication Committee • Section 9.2.8
Provided definition of Mean Calculated Bedtime in footnote	Correction	• Table 3
Clarified assessments to be conducted at Visits 6A and 6B	Correction	• Table 3 • Appendix 4, Extension Phase • Table 8
Revised Endpoints	To reflect exploratory nature of this Phase 2 study and align with objectives	• Synopsis • Statistical Methods • Sections 9.7.1.1 to 9.7.1.6

Revised visit windows during the Open-Label Extension Phase of the study (including footnotes on the Extension Schedule of Assessments) and added electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) to the End of Study Visit/Early Termination Visit	Correction and clarification	• Appendix 4, Extension Phase
		  • Design and Plan
		• Appendix 4, Extension Phase
		  • Table 8

Added study drug dispensing at Visit 8d	To correct an oversight as this is a clinic visit	• Appendix 4, Extension Phase • Table 8

Updated (reduced) sample size	For correction as fewer subjects are needed to achieve objectives	• Synopsis
		  • End of Core Study
		  • Number of Subjects
		  • Sample Size Rationale
		• Section 9.3
		• Section 9.7.2

Clarified the interim analysis procedure	To reflect change in analysis strategy	• Synopsis • Interim Analysis • Section 9.7.3

Revision History **Previous Version: v9.0** **Current Version: v10.0** **Date of Latest Revision: 20 June 2018 (revised per Amendment 06)**		
Added to the prohibited concomitant medication lis	Probibited moderate cytochrome P450 (CYP) 3A inhibitors	• Synopsis • Concomitant Drug Therapy • Section 7.1.4.3 • Section 9.4.7.2 • Appendix 3
Added information to Phase 1 study descriptions	Reported results of Study 012, which reported moderate CYP3A interaction	• Section 7.1.4.1
Updated Protocol Signature Page	Correction	• Protocol Signature Page

Revision History
Previous Version: v8.0
Current Version: v9.0
Date of Latest Revision: 17 Nov 2017 (revised per Administrative Change)

Change	Rationale	Affected Protocol Section(s)
Corrected typographical error	Maintain consistency	Synopsis • Efficacy assessments • Section 9.5.1.3

Revision History

Previous Version: v7.0

Current Version: v8.0

Date of Latest Revision: 17 Nov 2017 (revised per Amendment 05)

Change	Rationale	Affected Protocol Section(s)
Added an Extension Phase of up to 30 months specifying that eligible subjects who elect to receive open-label treatment after completing the End of Study (EOS) Visit will receive lemborexant (E2006) 5, 10, or 15 mg per day. A detailed description of the Extension Phase was added in Appendix 4. Revised references to Prerandomization and Randomization Phases to specify as the "Core Study."	Added to assess long-term safety and tolerability of lemborexant (E2006) 5, 10, or 15 mg per day. For clarity of presentation where description of the Extension Phase procedures have been added.	Synopsis • Title • Study Period • Investigators • Objectives • Study Design • Number of Subjects • Inclusion Criteria • Exclusion Criteria • Study Treatment • Duration of Treatment • Assessments • Statistical Methods • Study Endpoints • Efficacy Analysis • Pharmacokinetic Analysis • Safety Analysis • Section 7.1.4.1 • Section 8.1 • Section 9.1 • Section 9.1.2.1 • Section 9.1.3.1 • Section 9.1.3.2 • Section 9.1.4 • Section 9.2.4 • Section 9.3 • Section 9.3.1 • Section 9.3.2 • Section 9.4.1 • Section 9.5.1.2.3 • Section 9.5.1.3 • Section 9.5.1.4.1 • Section 9.5.1.5.4 • Section 9.5.1.5.8 • Section 9.5.2.1 • Section 9.5.4.1 • Section 9.7.1 • Section 9.7.1.1.1 • Section 9.7.1.1.3 • Section 9.7.1.6.1 • Section 9.7.1.6.2 • Section 9.7.1.8.6 • Section 9.7.3 • Appendix 3 • Appendix 4

Revision History
Previous Version: v7.0
Current Version: v8.0
Date of Latest Revision: 17 Nov 2017 (revised per Amendment 05)

Change	Rationale	Affected Protocol Section(s)
		• Protocol Signature page • Investigator signature page
Revised language to reflect changes in the actigraphy requirement		• Section 9.1.2.1 • Section 9.1.2.2 • Section 9.1.3.1
Revised inclusion criterion #8; updated actigraphy requirement	To facilitate enrollment	• Section 9.3.1 • Section 9.3.2
Revised the number of subjects screened	Reflects the actual study experience to date	• Section 9.3
Revised assessments of Neuropsychiatric Inventory – 10 Item (NPI-10), Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognitive (ADAS-cog), and Sleep Disorders Inventory (SDI) from the Safety Assessments for the Core Study, and to the Efficacy Assessments.	Correction	• Section 9.5.1.3 • Section 9.5.1.5 • Section 9.7.1.6.2 • Section 9.7.1.8.6
Correction of typos	Clarity	• Section 9.5.1.4.1
Revised the primary endpoint description and the primary endpoint analysis description to provide a statement detailing the change in analysis, ie, now based on 8-hour defined sleep period	Due to a change in definition of the baseline requirements	• Section 9.7.1.1.1 • Section 9.7.1.6.1
Revised to reflect addition of activity tracker	Updated the description of the Screening process with a new section, "Optional Prescreening" that details the addition of an activity tracker	Synopsis: • Optional Prescreening • Section 9.1.2.1
Revised signature pages	Inclusion of the EudraCT number	• Protocol Signature Page • Investigator Signature Page
Revised viral test from safety to Screening	Assessment is only performed during screening	• Section 9.5.1.2.3 • Section 9.5.1.5.8
Revised list of prohibited medications	Added orexin receptor antagonists	Appendix 3

Revision History

Previous Version: v6.0

Current Version: v7.0

Date of Latest Revision: 11 Oct 2017 (revised per Administrative Change)

Change	Rationale	Affected Protocol Section(s)
Updated SAE reporting information	Administrative change	• Section 9.5.4.1

Revision History
Previous Version: v5.0
Current Version: v6.0
Date of Latest Revision: 10 Aug 2017 (revised per Amendment 04)

Change	Rationale	Affected Protocol Section(s)
Revised protocol to include the conduct of the study in the European Union	To facilitate enrollment	• Title Page • Synopsis – Sites • Section 4 • Section 5.2 • Section 6 • Section 9.5.4.6 • Section 11.5
Revised total number of sites from approximately 40 to approximately 60	To facilitate enrollment	• Synopsis – Sites • Section 6 • Section 9.3
Revised sponsor signature page	To reflect current study sponsor approvers	• Sponsor Signature Page

Revision History

Previous Version: v4.0

Current Version: v5.0

Date of Latest Revision: 05 April 2017 (revised per Amendment 03)

Change	Rationale	Affected Protocol Section(s)
Revised inclusion (#4) MMSE lower end of range from 15 to 10	To allow for subjects with lower MMSE scores within the moderate range	• Synopsis – Inclusion Criteria • Section 9.3.1
Clarified inclusion (#5) that the report of ISWRD symptoms can be from the subject or caregiver	To be consistent with ICSD definition	• Synopsis – Inclusion Criteria • Section 9.3.1
Clarified exclusion (#20) the type of surgery that would be prohibited	For clarity	• Synopsis – Exclusion Criteria • Section 9.3.2
Clarified exclusion (#22) of concomitant treatments for ISWRD that are prohibited	For clarity	• Synopsis – Exclusion Criteria • Section 9.3.2 • Appendix 3
Revised the screening and baseline window	For flexibility in scheduling	• Synopsis – Study Design • Section 9.1 • Section 9.1.1.1 • Section 9.1.2.3 • Figure 3 • Table 3
Revised prohibited medications	To allow for subjects taking stable doses of medications used to treat ISWRD-related symptoms but who continue to manifest ISWRD symptoms	• Synopsis – Concomitant Drug/Therapy • Section 9.4.7.2
Clarified instructions Site are to give to subjects for actigraphy and log	For clarity	• Synopsis – Study Design • Section 9.1.1.1 • Section 9.5.1.3
Clarified measurement of cognitive enhancers for PK	For clarity	• Synopsis – Bioanalytical Methods • Section 9.5.1.4.1 • Table 2
Revised unit (days vs nights) for aWE throughout	For consistency throughout document	• Synopsis – Statistical Methods • Section 9.7.1.1.3
Revised Schedule of Assessments footnote assignments	For clarity	• Table 3
Revised footnotes to clarify testing for glucose	It is not required to measure fasting glucose in this protocol	• Appendix 1
Revised sponsor signature page	To reflect current sponsor representatives	• Sponsor Signature Page

Revision History **Previous Version: v3.0** **Current Version: v4.0** **Date of Latest Revision: 01 Mar 2017 (revised per Amendment 02)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised minimum criterion for actigraphy sleep efficiency from <75% to <85%	To be consistent with insomnia program	Synopsis – Inclusion Criteria Section 9.3.1
Revised definition of desired 8 hours sleep period	For clarity	• Synopsis – Study Design • Section 9.1.2.2
Revised time of day to complete the sleep log	To correct instructions	• Synopsis – Study Design • Section 9.1.2.2 • Section 9.5.1.3
Revised name and description of Adjudication Committee, and added potential seizures as adverse events to be adjudicated	As requested by FDA, to include information on potential seizures for adjudication as potential symptoms of cataplexy	• Synopsis – Study Design • Synopsis – Statistical Methods • Section 9.2.8
Added the requirement for monitoring of falls	Per request of FDA and to explicitly evaluate this safety parameter in at-risk population	Table 3
Revised List of Prohibited Concomitant Medications (Appendix 3)	To correct lists of strong CYP3A inhibitors and CYP3A inducers	Appendix 3
Revised text regarding ECG interpretation categories	For clarity	Section 9.7.1.8.5

Revision History
Previous Version: v2.0
Current Version: v3.0
Date of Latest Revision: 26 Jan 2017 (revised per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Modified primary objective wording	For consistency	Synopsis – Primary Objectives Section 8.1
Modified secondary objective wording	Correction	Synopsis – Secondary Objectives Section 8.2
Added allowance for caregiver informants and actigraphy data informants	For flexibility in caregiving situations without compromising data collection	Synopsis – Study Design, Inclusion Criteria for Caregivers, Statistical Methods Section 9.1 Section 9.1.2 Section 9.1.3 Section 9.3.1 Section 9.5.1.3 Table 3 Section 9.7.1.9
Added allowance for subjects to attend day care	For flexibility regarding daytime activities	Synopsis – Study Design Section 9.1
Added allowance for split baseline visits if necessary	For flexibility regarding scheduling	Synopsis – Study Design Section 9.1.2.3
Revised minimum age from 65 years to 60 years	To enhance inclusion of mild AD subjects, who tend to be younger	Synopsis – Inclusion Criteria for Subjects, Study Design Section 9.1 Section 9.3.1 Section 9.7.1.4
Revised title of Figure 2	For clarity	Section 7.1.1
Revised minimal MMSE score from 18 to 15	To enhance inclusion of subjects in the moderate range of AD	Synopsis – Inclusion Criteria for Subjects Section 9.3.1
Revised the requirement to remain in bed for at least 7 hours per night	To recognize that subjects may try to stay in bed, but may not be able to remain for the entire 7 hour period	Section 9.3.1
Revised the allowable residences for subjects	For clarity	Synopsis – Inclusion Criteria for Subjects Section 9.3.1
Added allowance for subjects with suicidal behavior in the past, but not within 10 years	To avoid excluding subjects unnecessarily	Synopsis – Exclusion Criteria for Subjects Section 9.3.2

Revision History
Previous Version: v2.0
Current Version: v3.0
Date of Latest Revision: 26 Jan 2017 (revised per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Added allowance for subjects with bundle branch block, if considered not clinically significant	For consistency across the lemborexant clinical program	Synopsis – Exclusion Criteria for Subjects Section 9.3.2
Added allowance for participate of subjects who are enrolled in observational studies without treatment components	To avoid excluding subjects unnecessarily	Synopsis – Exclusion Criteria for Subjects Section 9.3.2
Revised definition of Sleep Fragmentation Index	Correction	Synopsis – Assessments Section 9.5.1.3
Revised definition of Wake Fragmentation Index	Correction	Synopsis – Assessments Section 9.5.1.3
Revised pharmacodynamic analysis wording	Clarification that all PD variables are efficacy variables	Synopsis – Statistical Methods Section 9.7.1.7.2
Replaced the ADCS-CGIC with the Clinician's Global Impression of Change Irregular Sleep-Wake Rhythm Disorder (CGIC-ISWRD) Scale	To focus the clinical rating of improvement on the symptoms related to ISWRD	Synopsis – Secondary Objectives, Exploratory Objectives, Study Design, Efficacy Assessments, Statistical Methods Section 8.2 Section 8.3 Section 9.1.2.3 Section 9.1.3 Section 9.5.1.3 Table 3 Section 9.7.1.1.4 Section 9.7.1.6.2
Deleted "mean" from analysis of IV, IS, L5, M10, AMP and RA	Correction (as they are derived over 7 days)	Synopsis – Statistical Methods Section 9.7.1.7.2
Revised population for caregiver endpoints for caregivers who do not live with subject	To allow for analyses based on caregiving situations	Synopsis – Statistical Methods Section 9.7.1.9
Revised analysis of QT interval	Correction for consistency across lemborexant clinical program	Section 9.7.1.8.5
Added location of source data	For clarity	Section 11.5
Revised total number of sites from 25 to 40	To assist with enrollment	Synopsis – Number of Subjects Section 9.3

Revision History
Previous Version (Original): v1.0
Current Version (Revised original): v2.0
Date of Revisions: 19 Oct 2016

Change	Rationale	Affected Protocol Section(s)
Reworded title	To focus on the disorder of primary interest	Title page Synopsis – Study Protocol Title
Added relative amplitude of the rest-activity rhythm as a measure of the onset and course of treatment effect	For completeness of standard actigraphy measures	Synopsis – Objectives Synopsis – Assessments Synopsis – Statistical Methods Section 8.2 Section 8.3 Section 9.5.1.3 Section 9.5.1.4 Section 9.7.1.1.4 Section 9.7.1.1.5 Section 9.7.1.6.2 Section 9.7.1.7
Changed exploratory objective for health outcomes to include caregiver outcomes	To clarify that caregiver outcomes from the EQ-5D-5L will be part of the exploratory objectives	Synopsis -- Objectives
Added text to allow determination of plasma concentrations of other cognitive enhancers in addition to donepezil	Per regulatory feedback (FDA)	Synopsis – Objectives Synopsis – Study Design Synopsis – Assessments Synopsis – Bioanalytical Methods Synopsis – Statistical Methods Section 7.1.4.3 Section 8.3 Section 9.1.2.3 Section 9.5.1.4.1 Table 3 Section 9.7.1.1 Section 9.7.1.7
Replaced term “actiwatch” with “actigraph”	To ensure correct terminology	Synopsis, Study Design Synopsis -- Assessments Section 9.1.2 Section 9.1.3 Section 9.1.3.2 Section 9.5.1.3
Deleted statement regarding the need to log the time of actigraph removal	To clarify that only the times when the actigraph was returned to the wrist is required for the log	Synopsis -- Study Design Section 9.1.2 Section 9.5.3

Revision History **Previous Version (Original): v1.0** **Current Version (Revised original): v2.0** **Date of Revisions: 19 Oct 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Removed PSG and allowed for diagnostic sleep study to be conducted at home	To allow screening for sleep-disordered breathing from subjects who would not be able to tolerate being evaluated in a sleep laboratory setting	Synopsis – Study Design Synopsis – Exclusion Criteria for Subjects Section 9.1.2 Section 9.2.2 Table 3
Stipulated that central scoring will determine whether inclusion criteria quality standards have been met at screening	For clarity	Synopsis – Study Design Section 9.1.2
Stipulated that in addition to subjects, caregivers will also return to the clinic for the end of study visit	To correct omission	Synopsis – Study Design Section 9.1.3.2
Revised wording to clarify that the Follow-up Period will include the End of Study visit	For clarity	Synopsis – Study Design
Deleted distinction between mild and moderate AD-D as inclusion criteria	To clarify that the inclusion criteria are to be applied to the diagnosis of Alzheimer's disease, not to stage of disease	Synopsis – Inclusion Criteria for Subjects Section 9.3.1
Changed criterion frequency of complaints of sleep and wake fragmentation to ≥ 3 days per week	To correct a typographical error	Synopsis – Inclusion Criteria for Subjects
Changed criterion frequency for sleep-wake fragmentation recorded by actigraphy to ≥ 3 days per week	For consistency with history	Synopsis – Inclusion Criteria for Subjects Section 9.3.1
Clarified that central sleep apnea (as well as obstructive sleep apnea) is an exclusion criterion, and reworded definition	To ensure such patients are appropriately excluded	Synopsis – Exclusion Criteria for Subjects Section 9.3.2
Deleted the metric of >15 events per hour from the exclusion criterion, periodic limb movement disorder	Determined that the periodic limb movement index was not needed as an exclusion criterion	Synopsis -- Exclusion Criteria for Subjects Section 9.3.2 Table 3
Corrected exclusion criterion for Apnea-Hypopnea Index (can be equal to 15 events/hour or greater)	To be consistent with conventional definition of moderate sleep apnea	Synopsis -- Exclusion Criteria for Subjects Section 9.3.2

Revision History **Previous Version (Original): v1.0** **Current Version (Revised original): v2.0** **Date of Revisions: 19 Oct 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added text to clarify the interval during which designated medications will be prohibited	For consistency	Synopsis – Exclusion Criteria for Subjects Synopsis – Assessments Section 9.3.2
Stipulated that anticholinergic drugs are included in prohibited medications	For clarity	Synopsis – Concomitant Drug/Therapy Section 9.4.7
Added definition of an alcoholic drink	For clarity	Synopsis – Concomitant Drug/Therapy Section 9.4.7
Added details to instructions for use of rescue medications	Subject safety	Synopsis – Concomitant Drug/Therapy Section 9.4.7.2
Provided definition of phototherapy	For clarity	Synopsis – Concomitant Drug/Therapy
Provided definition of Sleep Fragmentation Index	For clarity	Synopsis – Assessments Section 9.5.1.3
Deleted "long" from definition of sleep bouts	For clarity	Section 9.5.1.3
Specified that the ADCS-CGIC will be administered by an independent rater who has no access to other data or scores	To minimize bias when the ADCS-GCIC is administered	Synopsis, Assessments Section 9.5.1.3
Deleted abbreviation, "aMeanDurLongAw" and inserted new abbreviations "aMeanDurWB"	To ensure correct abbreviation	Synopsis, Statistical Methods Section 9.7.1.1 Section 9.7.1.6
Changed wording for aSE endpoint, from "longer" to "higher"	To use appropriate unit of measurement	Synopsis, Statistical Methods Section 9.7.1.1
Corrected year of Mishima et al. reference	To correct editorial error	Synopsis, Statistical Methods Section 9.7.1.2
Updated list of abbreviations	For consistency with changes in text	Section (List of Abbreviations)
Added statement to stipulate that subject and caregiver should be informed if there is new information relevant to their study participation	To be consistent with information shared with participants in the informed consent forms	Section 5.3
Added that the subject will complete the EQ-5D-5L but not the SDI	To correct error (SDI completed by caregiver)	Section 9.1.2.3

Revision History **Previous Version (Original): v1.0** **Current Version (Revised original): v2.0** **Date of Revisions: 19 Oct 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Provided that the site on the arm where the actigraph is applied will be examined	Safety of subjects – look for possible local irritation	Section 9.1.3
Provided that at the end of study visit, actigraphy data and the sleep log will be transmitted to a central reader	For consistency with other study visits and to correct an omission	Section 9.1.3.2
Corrected wording of eC-SSRS exclusion criterion	For consistency	Section 9.3.2
Corrected description of blister containers; "packs" not "blisters"	Updated on basis of new packaging information	Section 9.4.2
Provided that a medical registration number in the PI curriculum vita can substitute for a copy of the PI's medical license	To allow flexibility in collection of PI information	Section 9.4.9
Added text explaining the method of scoring data from an actigraph	For clarity of instruction	Section 9.5.1.3
Specified blood sample volumes and timing and method of collection for plasma concentration of cognitive enhancers	To list appropriate volumes following additional of assessments of all cognitive enhancers and to correct mistake in addition	Section 9.5.1.4 Table 3
Deleted bands from hematology tests	This test is not needed	Table 1
Revised blood sampling volume instructions to indicate that the specified volume is approximate, and added collection time points for Visit 5	To allow flexibility in the collection of blood sample volumes, and provide details of timing	Table 2
Deleted cross-reference from EOS to footnote "c"	To correct an inaccuracy, as subjects who discontinue will undergo an early termination visit	Table 3
In footnote, specified that at least 2 days must intervene between screening and the Baseline Visit.	For consistency	Table 3
Clarified that sample collection for PG analysis is not required	To address requirement in Japan for samples to be optional	Appendix 2
Updated list of strong CYP3A4 inhibitors	For completeness	Appendix 3

Revision History **Previous Version (Original): v1.0** **Current Version (Revised original): v2.0** **Date of Revisions: 19 Oct 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added Yi-gan-sun to the list of prohibited medications	For completeness	Appendix 3
Corrected occurrences of abbreviation definitions	Editorial quality	Various

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2006-G000-202
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia (revised per Amendment 05)
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK (revised per Amendment 04) Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112-8088 Japan
Investigational Product:	Lemborexant (E2006)
Indication:	Irregular Sleep-Wake Rhythm Disorder
Phase:	2
Approval Date:	V1.0 11 Aug 2016 (original protocol) V2.0 19 Oct 2016 (revised original protocol) V3.0 26 Jan 2017 (revised per Amendment 01) V4.0 01 Mar 2017 (revised per Amendment 02) V5.0 05 Apr 2017 (revised per Amendment 03) V6.0 10 Aug 2017 (revised per Amendment 04) V7.0 11 Oct 2017 (revised per Administrative Change) V8.0 17 Nov 2017 (revised per Amendment 05) V9.0 17 Nov 2017 (revised per Administrative Change) V10.0 20 Jun 2018 (revised per Amendment 06)
IND Number:	130798
EudraCT Number:	2017-003306-40 (revised per Amendment 04)
GCP Statement:	This study is to be performed in full compliance with International Council for 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 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia (revised per Amendment 05)
Investigators (revised per Amendment 05) **Core Study and Extension Phase:** Investigators in North America, European Union, and Japan
Sites Approximately 60 sites in North America, European Union, and Japan (revised per Amendments 01 and 04)
Study Period and Phase of Development (revised per Amendment 05) Core Study: Approximately 18 months Extension Phase: Up to 30 months, or until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued.
Objectives (revised per Amendments 05 and 06) <u>Sleep-Related Objectives</u> ◦ To determine the dose response of lemborexant 2.5 mg (LEM2.5), 5 mg (LEM5), 10 mg (LEM10) and 15 mg (LEM15) compared to placebo (PBO) on the change from baseline in actigraphy-derived Sleep Efficiency (aSE) during the last week of treatment in subjects with ISWRD and Alzheimer's disease dementia (AD-D). (revised per Amendments 01 and 06) ◦ To determine the efficacy of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO on the change from baseline of aSE during each week of treatment. (revised per Amendment 06) ◦ To determine the efficacy of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO on the change from baseline on the Sleep Fragmentation Index (SFI) during each week of treatment. (revised per Amendment 06) ◦ To determine the change from baseline of the mean duration of wake bouts (aMeanDurWB) over each week of treatment. (revised per Amendment 06) <u>Wake-Related Objectives</u> ◦ To determine the dose response of lemborexant 2.5 mg (LEM2.5), 5 mg (LEM5), 10 mg (LEM10) and 15 mg (LEM15) compared to placebo (PBO) on the change

from baseline in actigraphy-derived Wake Efficiency (aWE) during the last week of treatment in subjects with ISWRD and Alzheimer's disease dementia (AD-D). (revised per Amendments 01 and 06)

- To determine the efficacy of lemborexant LEM2.5, LEM5, LEM10 and LEM15 compared to PBO on the change from baseline of actigraphy-derived Wake Efficiency (aWE) during each week of treatment. (revised per Amendment 06)
- To determine the efficacy of LEM2.5, LEM5, LEM10, and LEM15 compared to PBO on the change from baseline of Wake Fragmentation Index (WFI) during each week of treatment. (revised per Amendments 01 and 06)
- To determine the change from baseline of the mean duration of sleep bouts (aMeanDurSB) over each week of treatment. (revised per Amendment 06)

Circadian Rhythm-Related Objectives

- Onset and course of treatment effect as measured by change from baseline of intradaily variability (IV), interdaily stability (IS), amplitude of the rest-activity rhythm (AMP), relative amplitude of the rest-activity rhythm (RA), and other actigraphy variables during each week of treatment (revised per Amendment 06)

Additional Objectives (revised per Amendment 06)

- To evaluate the safety and tolerability of lemborexant.
- To explore the effects of LEM2.5, LEM5, LEM10, LEM15 and PBO at the end of 4 weeks of treatment (unless otherwise specified) on the following:
  - Change from baseline of sum of activity counts and number of bouts >10 minutes of sleep in the first 3 hours after morning waketime on each of the first 3 days and last 3 days of treatment as an indicator of next-morning residual effects.
  - Potential rebound ISWRD in the 2 weeks following 4 weeks of treatment.
  - Change from baseline in Clinician's Global Impression of Change-ISWRD (CGIC-ISWRD) Scale on symptoms of ISWRD total score and domains. (revised per Amendments 01 and 06)
  - Change from baseline of Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog).
  - Change from baseline of Mini Mental State Examination (MMSE).
  - Change from baseline of sleep quality in caregivers as measured by the Pittsburgh Sleep Quality Index (PSQI).
  - Change from baseline of caregiver burden on the Zarit Burden Interview – short form (ZBI).
  - Change from baseline of health outcomes of the subject and/or caregiver on the EuroQOL version 5D-5L (EQ-5D-5L) (subject Self Version, caregiver Self Version, caregiver Proxy 1 Version).
  - Change from baseline of Mood and behavior on the Neuropsychiatric Inventory (NPI-10; by caregiver as proxy for the subject).
  - Change from baseline of on the Sleep Disorders Inventory (SDI; by caregiver as proxy for the subject).

- Characterize the pharmacokinetics (PK) of lemborexant using the population approach.
- To explore the PK/pharmacodynamic (PD) relationship between exposure to lemborexant and selected efficacy variables and most frequently occurring treatment-emergent adverse events (TEAEs).
- To assess the plasma concentrations of cognitive enhancers (cholinesterase inhibitors and/or memantine) and lemborexant in subjects taking such drugs.
- To evaluate the long-term safety and tolerability of flexible doses of LEM5, LEM10, and LEM15 per day over a period of 30 months in subjects with ISWRD who have completed the Core Study. (revised per Amendments 05 and 06)

Study Design (revised per Amendment 05)

This study will consist of a Core Study and an Open-Label Extension Phase.

Core Study

E2006-G000-202 is a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of lemborexant (4 dose levels) or PBO taken daily for 4 weeks in approximately 60 male or female subjects, ages 60 to 90 years, with mild or moderate AD-D who complain of disrupted sleep or multiple awakenings at night along with frequent periods of falling asleep during the day that impact the quality of life of the subject. For each subject, an individual who knows the subject well and will provide the information about themselves will also be enrolled in the study (Caregivers and Informants – see below). Additional Informants may also be associated with the study, but will not be required to complete a consent form. (revised per Amendments 01 and 06)

The study will have 3 phases: the Prerandomization Phase, the Randomization Phase, and the Extension Phase. The Prerandomization Phase will comprise 2 periods that will last up to a maximum of 42 days: a Screening Period and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects will be treated for 4 weeks, and a minimum 14-day Follow-Up Period before an End of Study visit. The Extension Phase will consist of a 30-month Maintenance Period and a 14-day Follow-Up Period. (revised per Amendments 03 and 05)

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

Subjects will not be excluded if they attend adult day care as long as the day care staff can ensure that the actigraph remains on the subject's wrist and, if removed, is returned as promptly as possible, with notation of the time of the replacement noted for inclusion on the sleep log. (revised per Amendment 01)

<u>Caregivers and Informants (revised per Amendment 01)</u>

For the subject to participate in the study, there must be 1 or more persons who can provide the required information for assessments, complete the sleep log, and ensure that the subject is dosed at the appropriate time. These roles can be fulfilled by the same or different individuals. For each subject, one individual will be designated as the "caregiver informant" (or "caregiver"), who will be sufficiently familiar with the subject to provide information to the site staff with respect to the subject's sleep and wake patterns, behavior, mood, AEs, and quality of life. Typically, the caregiver informant will need to spend at least 10 hours per week with the subject.

If the caregiver informant does not reside with the patient, then the other informant(s) will be responsible for ensuring that the sleep log is completed daily and that dosing occurs at the appropriate time. There can be more than one such informant, as in the case of home health aides who stay with the subject during the week and change on the weekend.

If the individual who is originally designated as the caregiver informant cannot fulfill the function, he/she may be replaced by a suitable alternate until the Baseline Visit, and thereafter only following consultation with the Sponsor.

Optional Prescreening

There may be circumstances where the subject and/or caregiver is not sure whether the subject has an ISWRD pattern of sleep and wake, and would benefit from reviewing a report on the subject's sleep/wake pattern before agreeing to participate in the study. In these cases, the sites can offer the subject an opportunity to wear a designated activity tracker before consenting to the rest of the study procedures. A separate prescreening consent form would be signed by the subject and his/her legal representative for this purpose. After wearing the device for approximately 4 days, the subject and caregiver would be scheduled to return to the clinic so that the output from the device can be reviewed. At that time, the subject and caregiver would decide whether to participate in the study, which will require the study consent forms to be completed as described above. (revised per Amendment 05)

Screening Period

The maximum duration of the Screening Period will be 42 days. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and caregiver and before the conduct of any screening procedures or assessments. Subjects or their legal representative will sign informed consent; caregivers must sign a separate consent form. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep Wake Type. The clinician will confirm that the subject meets diagnostic criteria for AD-D, based on the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines. If necessary, investigators may order a computed tomography (CT) scan and relevant blood tests to rule out other possible causes of dementia. Subjects will be administered the MMSE and the electronic Columbia -Suicide Severity Rating Scale (eC-SSRS), and will undergo the subject component of the Cornell Scale for Depression in Dementia (CSDD) interview. Additional eligibility criteria and clinical laboratory tests, ECG, vital signs, height, and weight will be assessed. Caregivers will be administered the caregiver input component of the CSDD. (revised per Amendments 03 and 05)

Eligible subjects will be provided with an actigraph to wear continuously throughout the study. They will be asked to provide a typical (habitual) time when the subject goes to sleep at night. (revised per Amendments 02 and 05)

The appropriate informants will be provided with a daily log (sleep log) to note the start and end times of the subject's actual time in bed each day during the night, and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. The informants will be trained in the use of the actigraph and the log. Site staff will instruct informants (1) in the evening, to fill in the times when the actigraph was not worn; and (2) in the morning, to fill out the bedtimes and morning rise times, and will emphasize the importance of doing so. Sites will also arrange for the subject to undergo a diagnostic sleep study either at a sleep center or at home, to determine the presence or absence of sleep apnea, unless a diagnostic sleep study has been obtained within the previous 6 months. Before randomization, the investigator will be required to review a report detailing the subject's apnea-hypopnea index. (revised per Amendments 01, 02, 03, and 05)

After subjects have had the actigraph for at least 14 days, caregivers will return to the clinic. The actigraph data will be downloaded and transmitted to the central reader along with the sleep log of bedtimes, morning waketimes, and the approximate times when the actigraph was replaced on the subject's wrist. Adverse event and concomitant medication use will be recorded. The sites will keep the actigraph at the clinic until the Baseline visit, when the device will again be provided to the subjects. The central scoring will determine whether the data from the screening period meet the quality standards required by the inclusion criteria. (revised per Amendments 01 and 05)

During the Screening Period, subjects who meet the eligibility criteria for ISWRD on the basis of actigraphy and are not excluded on the basis of the diagnostic sleep study for sleep apnea will then be scheduled for the Baseline visit. Subjects who did not meet eligibility criteria based on actigraphy may be rescreened following consultation with the Sponsor as long as they were not excluded based on the apnea-hypopnea index (AHI). (revised per Amendment 05)

Baseline Period

On Day 1, the Screening Period will end and the Baseline Period will take place. The Baseline visit must occur no earlier than 2 days and no later than 27 days after Visit 2 (caregiver visit), and may be scheduled across 2 consecutive days if necessary. Clinical laboratory tests, an ECG, vital signs, and weight will be assessed. Adverse events and concomitant medications will be queried and the site on the arm where the actigraph is applied will be examined. A plasma sample will be obtained from any subject taking one or more cognitive enhancers and will be used to measure plasma concentrations of the cognitive enhancer(s). As proxy for the subject, caregivers will complete the SDI, EQ-5D-5L (Proxy 1 Version), and the NPI-10. The caregiver will also complete the self-version of the EQ-5D-5L, the ZBI, and the PSQI for himself/ herself. The subject will be administered the ADAS-cog and the EQ-5D-5L (Self version). The CGIC-ISWRD rater will complete the baseline assessment for the Clinician's Global Impression of Change -ISWRD Scale. (revised per Amendments 01 and 03)

Treatment Period

The Treatment Period will begin on the evening of Day 1 and will continue for 4 weeks. Subjects will be randomized, in a double-blind manner, to receive LEM2.5, LEM5, LEM10, LEM15, or PBO. Study drug will be dispensed to the caregiver. During the Treatment Period, subjects will take study drug each night immediately (ie, within 5 minutes) before bedtime (defined as the median calculated bedtime [MCB]) calculated based on the sleep log during Screening. Time of dosing will be collected on the sleep log and entered into the appropriate electronic case report form (eCRF) by the sites.(revised per Amendments 01 and 05)

After approximately 2 weeks of the Treatment Period, caregivers and subjects will return to the clinic. The actigraph data will be downloaded and transmitted to the central reader along with the sleep log. Vital signs will be assessed at this visit. AEs, treatment compliance, and concomitant medication use will be recorded. The site on the arm where the actigraph is applied will be examined.

If the subject experiences an AE that results in a temporary discontinuation of study medication, a rechallenge is possible following consultation with the Medical Monitor. (revised per Amendment 05)

At the end of 4 weeks, subjects will return to the clinic with their caregivers for end of Treatment Period assessments. Clinical laboratory tests, an ECG, vital signs, and weight will be assessed, and AEs and concomitant medications will be recorded. The site on the arm where the actigraph is applied will be examined. Treatment compliance will be assessed. As proxy for the subject, caregivers will complete the SDI, the NPI-10 and the EQ-5D-5L (Proxy 1 Version). The caregiver will also complete the EQ-5D-5L (Self Version), ZBI-short, and PSQI for himself/ herself. Subjects will be administered the MMSE, EQ-5D-5L (Self Version), ADAS-cog, and eC-SSRS. A PK sample

will be obtained. The CGIC-ISWRD Scale rater will complete the CGIC-ISWRD Scale. The actigraph data will be downloaded and transmitted to the central reader along with the sleep log, and the actigraph will be returned to the subject for the Follow-Up Period. (revised per Amendment 01)

During the End of Treatment visit, the study staff will discuss the Extension Phase with potentially eligible subjects and caregivers. (revised per Amendment 05)

Follow-Up Period

The Core Study Follow-Up Period will begin when subjects leave the clinic at the end of the Treatment Period. Subjects will cease taking study drug but will continue to wear the actigraph until the End of Study visit. (revised per Amendment 05)

At least 14 days but no more than 18 days after the end of the Treatment Period, subjects and caregivers will return to the clinic for the End of Core Study Visit. Clinical laboratory tests, an ECG, vital signs, and weight will be assessed, and AEs and concomitant medications will be recorded. The site on the arm where the actigraph is applied will be examined. Actigraphy data will be downloaded and transmitted to the central reader along with the sleep log. (revised per Amendment 05)

A subject who prematurely discontinues taking study drug should return to the clinic as soon as possible after discontinuing study drug, to complete an Early Termination Visit and a Follow-Up Visit after 14 days. If the subject discontinues from the study due to an AE, the subject must complete an Early Termination Visit, and the AE must be followed to resolution or for 2 weeks, whichever comes sooner. (revised per Amendment 05)

Adjudication Committee (revised per Amendments 02 and 06)

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 Amendments 02 and 06)

End of Core Study (revised per Amendment 05)

Estimates for end of study are as follows:

- The study will begin in approximately December 2016.
- The end of the study will be the date of the last study visit for the last subject in the study.
- Approximately 60 subjects (60 to 90 years) with ISWRD will be randomized to lemborexant or PBO for 4 weeks (revised per Amendments 01 and 06)
- The estimated duration for each subject in the Core Study is anticipated to be a maximum of 93 days/13.3 weeks (Screening Period maximum of 42 days plus Treatment Period [maximum 33 days] plus Follow-Up Period [maximum 18 days including End of Study visit]). (revised per Amendments 03 and 05)

Extension Phase (revised per Amendment 05)

The Extension Phase comprises a 30-month Maintenance Period and a 14-day Follow-Up Period.

Design and Plan

Subjects who complete the Core Study End of Study (EOS) Visit within 30 days prior to enrollment in the Extension Phase will be eligible for participation. Subjects who complete the Core Study, but who do not elect to immediately continue into the Extension Phase, have up to 30 days after the End of Study Visit to enroll. Such subjects will be required to return to the site within 30 days of completion of the Core Study, and will repeat selected assessments before being dispensed drug for the Extension Phase.

Maintenance Period

During the Maintenance Period, all subjects initially will receive lemborexant 10 mg/day (LEM10). At the discretion of the investigator, subjects will have the option of increasing the dose to lemborexant 15 mg/day (LEM15) or decreasing the dose to lemborexant 5 mg/day (LEM5). All dose adjustments will be performed at an Unscheduled Visit or at the next scheduled visit. The dose can be adjusted more than once during the Extension Phase.

All doses will be taken orally in tablet form each night for the duration of the Extension Phase immediately (ie, within 5 minutes) before the time the subject intends to sleep. Subjects will receive 1 or 2 tablets as described below:

- LEM5: one lemborexant 5-mg tablet
- LEM10: one lemborexant 10-mg tablet
- LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet

Study visits, either in person or by telephone, will be conducted according to the Schedule of Procedures and Assessments for the Extension Phase. If the phone visit indicates an ongoing AE, the subject should be brought to the clinic for an Unscheduled Visit. Subjects may discontinue from study drug for any reasons. A subject who prematurely discontinues taking study drug should return to the clinic within 2 weeks of discontinuation to complete an Early Termination Visit. The assessments of the Early Termination Visit are the same as those for the EOS Visit of the Core Study. If the subject discontinues from the study due to an AE, the subject must complete an Early Termination Visit, and the AE must be followed to resolution or for a period of 4 weeks, whichever comes sooner.

Follow-up Period

The Follow-Up Period will be 14 to 18 days in duration, and begins when subjects leave the clinic at the end of the Maintenance Period. At least 14 days but no more than 18 days after the end of the Maintenance Period, subjects and caregivers will return to the clinic for the End of Study Visit, including the recording of AEs and concomitant medications, and assessment of clinical laboratory tests, vital signs and weight, suicidality, and will undergo an ECG.

Treatment in the Extension Phase will last for a maximum duration of 30 months, until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued.

Number of Subjects

It is expected that approximately 230 subjects will be screened to provide 60 randomized subjects. (revised per Amendment 06)

Subjects will be randomized to one of the following treatment arms: PBO, LEM2.5, LEM5, LEM10, or LEM15, in an approximate 1:1:1:1:1 ratio, stratified by country. (revised per Amendment 05)

Inclusion Criteria for Subjects (Core Study) (revised per Amendment 05)

1. Male or female, age 60 to 90 years at the time of informed consent (revised per Amendment 01)
2. Able to provide informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, if required in accordance with local laws, regulations and customs, and the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations).
3. Documentation of diagnosis with AD-D on the basis of the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines
4. MMSE 10 to 26 at Screening (revised per Amendments 01 and 03)
5. Meets criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (Diagnostic and Statistical Manual of Mental Disorders – 5th edition [DSM-5]) and the 10th revision of the International Classification of Diseases (ICD-10), as follows: Complaint by the subject or caregiver of difficulty sleeping during the night and/or excessive daytime sleepiness associated with multiple irregular sleep bouts during a 24-hour period (revised per Amendment 03)
6. Frequency of complaint of sleep and wake fragmentation ≥3 days per week
7. Duration of complaint of sleep and wake fragmentation ≥3 months
8. During the Screening Period, mean aSE <87.5% within the defined nocturnal sleep period and mean aWE <87.5% during the defined wake period (revised per Amendments 02 and 05)
9. Confirmation by actigraphy of a combination of sleep bouts of >10 minutes during the wake period plus wake bouts of >10 minutes during the sleep period, totaling at least 4 bouts per 24 hours period, ≥ 3 days per week
10. Ambulatory and living in the community or in a residence not classified as a skilled nursing facility (an assisted living facility with separate living quarters where subjects and their caregivers reside is acceptable) (revised per Amendment 01)
11. Willing not to start a behavioral or other treatment program for sleep or wake difficulties and not to start a new treatment for other symptoms of AD-D during participation in the study
12. Has a reliable and competent caregiver (or caregiver and informants) who can accompany the

subject to study visits, administer study medication on a nightly basis and provide information on the status of the subject (revised per Amendment 01)

13. For subjects taking a cholinesterase inhibitor and/or memantine, dosing regimen must have been stable for at least 3 months

Inclusion Criteria for Caregivers

14. Able to provide informed consent
15. Spends at least 10 hours per week with the subject (revised per Amendment 01)
16. Able to meet caregiver requirements (Subject inclusion criterion #13)
17. Willing to provide information on himself/herself regarding sleep quality and caregiver burden

Inclusion Criteria for Subjects (Extension Phase) (revised per Amendment 05)

1. Completed the Core Study (EOS Visit). Subjects who participated in the Core Study and completed the EOS Visit within 30 days may return to participate in the Extension Phase as long as there are no contraindications due to ongoing adverse events or prohibited medications. (revised per Amendment 05)

Exclusion Criteria for Subjects

1. A diagnosis of vascular dementia, dementia following multiple strokes, or any synucleinopathy / Lewy body disorder. This includes Dementia with Lewy Bodies and Parkinson's disease with or without dementia.
2. A current diagnosis of moderate to severe obstructive sleep apnea (OSA) or central sleep apnea, or current use of continuous positive airways pressure even if mild severity of OSA, restless legs syndrome, periodic limb movement disorder (with awakenings), or narcolepsy
3. An Apnea-Hypopnea Index or equivalent ≥15 events/hour on diagnostic sleep study conducted prior to Baseline or within 6 months of Screening
4. A clinically significant movement disorder that would affect the differentiation of sleep and wake by the actigraphy analytic algorithm
5. Current symptoms or history during the past year of Rapid Eye Movement (REM) Behavior Disorder or sleep-related violent behavior
6. Probable Major Depression, as evidenced by score >10 on the CSDD at Screening
7. Unable to tolerate wearing the actigraph. At a minimum, subjects must be able to wear the actigraph for 5 complete days out of 7 days' data. A day will be considered complete as long as data from 90% of the 24-hour period are able to be scored.
8. Excessive caffeine use that in the opinion of the investigator contributes to the subject's ISWRD
9. History of drug or alcohol dependency or abuse within approximately the previous 2 years
10. Reports habitually consuming more than 14 drinks containing alcohol per week or habitually consumes alcohol within 3 hours before bedtime and 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
11. Known to be human immunodeficiency virus positive
12. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
13. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms) (subjects with evidence of bundle branch block are not excluded if the block is not clinically significant, as

documented by the investigator in the source document) (revised per Amendment 01)

14. Current evidence of clinically significant disease that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
15. Any history of a medical or psychiatric condition other than Alzheimer's Disease dementia that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
16. History of malignancy within the previous 5 years except for adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ
17. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 and 5 on the Suicidal Ideation section of the eC-SSRS
18. Any suicidal behavior within the past 10 years based on the eC-SSRS (revised per Amendment 01)
19. History of violence toward the caregiver or others
20. Scheduled for surgery using general anesthesia during the study (revised per Amendment 03)
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before starting actigraphy during Screening. (A list of prohibited concomitant medications is presented in Appendix 3 of the protocol.)
22. Used any modality of treatment for ISWRD between Screening and Randomization based on approaches related to circadian rhythms, including phototherapy (light therapy), melatonin and melatonin agonists (revised per Amendment 03)
23. Failed treatment with Belsomra® (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones between Screening and Randomization, or plans to travel across more than 3 time zones during the study
25. Hypersensitivity to lemborexant or to its excipients
26. Currently enrolled in another clinical trial, except for observational studies with no treatment component (revised per Amendment 01)
27. Used any investigational drug or device before informed consent (ie, within 30 days or 5× the investigational drug half-life whichever is longer or 6 months for potential disease-modifying drugs)
28. Previously participated in any clinical trial of lemborexant

Study Treatment(s)

Lemborexant 2.5 mg, 5 mg, 10 mg, 15 mg, or lemborexant-matched PBO treatments will be taken orally in tablet form each night for 28 consecutive nights immediately (ie, within 5 minutes) before the time the subject intends to try to sleep. All subjects will receive 2 tablets as described below, according to the treatment arm to which the subject has been randomized:

LEM2.5: one lemborexant 2.5-mg tablet and one lemborexant-matched placebo tablet

LEM5: one lemborexant 5-mg tablet and one lemborexant-matched placebo tablet

LEM10: one lemborexant 10-mg tablet and one lemborexant-matched placebo tablet

LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet

PBO: two lemborexant-matched placebo tablets

Extension Phase (revised per Amendment 05)

During the Maintenance Period, all subjects initially will receive lemborexant 10 mg per day (LEM10). At the discretion of the investigator, subjects will have the option of increasing the dose to lemborexant 15 mg per day (LEM15) or decreasing to lemborexant 5 mg per day. All dose adjustments will be performed at an unscheduled visit or at the next scheduled visit. The dose can be adjusted more than once during the Extension Period.

All doses will be taken orally in tablet form each night for the duration of the Extension Phase, immediately (ie, within 5 minutes) before the time the subject intends to sleep. Subjects will receive 1 or 2 tablets as described below:

- LEM5: one lemborexant 5-mg tablet
- LEM10: one lemborexant 10-mg tablet
- LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet

Duration of Treatment (revised per Amendment 05)

Core Study: A maximum of approximately 4 weeks

Extension Phase: Up to 30 months, or until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued.

Concomitant Drug/Therapy

Potential subjects who are taking a cholinesterase inhibitor and/or memantine will be allowed in the study provided that the treatment regimen has been stable for at least 3 months.

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.

Prohibited medications include anticholinergic drugs, moderate and strong CYP3A inhibitors and all CYP3A inducers. Prohibited therapies include any treatment for ISWRD that is based on modifying circadian rhythms, including bright light therapy, melatonin and melatonin agonists. In this context, phototherapy refers specifically to the use of timed bright light as a therapeutic intervention. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants). (revised per Amendments 03 and 06)

Medications that are used to treat behaviors associated with ISWRD, such as antipsychotic medications or trazodone, are permitted provided that the subject has been taking a stable dose for at least 1 month. (revised per Amendment 03)

If a medication is not on the list of prohibited medications but, in the opinion of the investigator, causes or exacerbates the subject's ISWRD, 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 study 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 that would compromise the safety of the subject, he/she must discontinue from the study, with the exception that certain prohibited

medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that moderate and strong CYP3A inhibitors and CYP3A4 inducers will not be permitted at any time for any duration during the study. (revised per Amendment 06)

If not used daily, benzodiazepines and non-benzodiazepine hypnotics and antipsychotics may be used as rescue medications to treat significant agitation or anxiety. The lowest effective dose should be used, for the shortest effective period of time, and for no more than 3 days per week. Before prescribing, whenever practicable, the investigator should discuss the proposed rescue medication with the Medical Monitor. If a rescue medication has been taken within 24 hours of a scheduled study visit, the timing of this visit should be adjusted. (revised per Amendment 03)

Phototherapy is prohibited during the study. In this context, phototherapy refers specifically to the use of timed bright light as a therapeutic intervention.

Assessments

Efficacy Assessments (revised per Amendment 05)

Actigraphy

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

A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the caregivers. The actigraphy data obtained during the Screening Period will be used to a) determine eligibility and b) derive baseline actigraphy parameters for those subjects who are randomized. The nocturnal sleep period will be defined for each subject as the 8 hours starting with the subject's MCB, calculated from the sleep log completed during screening. (revised per Amendment 05)

Also note that the calculated MCB will determine time of dosing for a given subject such that the dose each night should be taken within 5 minutes before bedtime. (revised per Amendment 05)

- Sleep efficiency (aSE): 100% × the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period, divided by 8 hours (revised per Amendment 05)
- SFI from actigraphy: The SFI will be calculated as the sum of a Movement Index (MI) and a Fragmentation Index (FI), with MI = (epochs of wake per TIB)*100 and FI = (number of ≤1 minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period)*100 (revised per Amendments 01 and 05)
- WFI from actigraphy: The WFI will be calculated as the sum of an Immobility Index (II) and a FI, with II = (epochs of immobility per the 16 hours outside of the defined sleep period)*100 and FI = (number of ≤1-minute periods of mobility/total number of periods of mobility of all durations during the 16 hours outside of the defined sleep period)*100 (revised per Amendments 01 and 05)
- aWE: 100% × the total duration of wake epochs during the defined wake period (ie, the 16 hours outside of the predefined sleep period) divided by 16 hours (revised per Amendment 05)
- Mean Duration of Wake Bouts (aMeanDurWB): average duration of all wake bouts (with wake bout defined as continuous wake of 10 minutes or longer) that occur during the predefined nocturnal sleep period (revised per Amendment 05)
- Mean Duration of Sleep Bouts (aMeanDurSB): average duration of all sleep bouts (with sleep bout defined as continuous sleep of 10 minutes or longer) that occur during the 16 hours outside of the predefined nocturnal sleep period (revised per Amendments 01 and 05, and Administrative Change)
- Intradaily Variability (IV): gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, with a higher number indicating more fragmentation; derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance)
- Interdaily Stability (IS): gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability); derived by the ratio between

the variance of the average 24-hour pattern around the mean and the overall variance

- L5: the average activity across the least active 5-hour period per 24 hour period with high values indicating restlessness
- M10: the average activity during the most active 10-hour period per 24 hour period, with low levels indicating inactivity
- AMP: amplitude of the rest-activity rhythm calculated as the difference between M10 and L5
- RA: relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5.

CGIC-ISWRD Scale (revised per Amendment 01)

The CGIC-ISWRD Scale uses the standardized methodology for obtaining global clinical ratings, and is an assessment conducted at the end of the treatment period by an independent rater who has no access to the source data or other psychometric test scores conducted as part of the given protocol. The instrument consists of 3 parts: a guided baseline interview administered to the subject and an informant, a follow-up interview administered to the subject and an informant, and a clinician's rating review. The informant must be a person who knows the subject well. The baseline interview serves as a reference for future ratings. During the baseline interview, the rater will evaluate subjects regarding domains of (1) sleep and wake symptoms; (2) mood and behavioral symptoms; (3) attention/arousal; and (4) social functioning. In the follow-up interview, a 7-point scale is used, from 1 = marked improvement, 4 = no change, to 7 = marked worsening, to score each of the four domains and to provide an overall score. The overall score is used to address the secondary objective; the domain scores are exploratory. In this study, the assessment will focus on the symptoms of ISWRD, not the general condition of dementia. (revised per Amendment 01)

Neuropsychiatric Inventory (NPI-10)

The NPI-10 assesses a wide range of behaviors seen in dementia for both frequency and severity. These include delusions, agitation, depression, irritability and apathy. The scale takes approximately 10 minutes for a clinician to administer. This scale will be administered with the caregiver as proxy for the subject. The NPI-10 has good psychometric properties and is widely used in drug trials. (revised per Amendment 01; revised to be an efficacy assessment in Amendment 05)

Mini Mental State Examination

The MMSE is a cognitive instrument commonly used for screening purposes. It is a 30-point scale with higher scores indicating less impairment and lower scores indicating more impairment. Seven items are assessed that measure orientation to time and place, registration, recall, attention, language, and drawing. The MMSE will be administered to the subject by site staff. (Revised to be an efficacy assessment in Amendment 05)

Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog)

The ADAS-cog is the most widely used cognitive scale in Alzheimer's disease trials. It is a structured scale that evaluates memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, ability to remember test instructions, maze, and number cancellation are also obtained. The modified version (ADAS-cog-13) used in this study is scored from 0 to 90 points with a score of 0 indicating no impairment, and a score of 90 indicating maximum impairment. (Revised to be an efficacy assessment in Amendment 05)

Sleep Disorders Inventory (SDI)

The SDI is an expanded version of one item of the NPI. It describes the frequency, severity, and caregiver burden of sleep-disturbed behaviors during a period prior to its administration. The SDI consists of the seven subquestions from the NPI sleep disturbance item. Each of the subquestions is a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-participant for the 2 weeks prior to the visit. (Revised to be an efficacy assessment in Amendment 05)

Pharmacokinetic Assessments (Core Study only) (revised per Amendment 05)

A blood sample for plasma concentrations of lemborexant and its metabolites M4, M9 and M10 will be taken at the end of treatment visit. The time and date of the 2 most recent doses before this sample and the time and date of the sample will be documented.

One blood sample (approximately 4 mL) will be obtained at Baseline (Visit 3) for only those subjects taking specific cognitive enhancers (ie, donepezil or galantamine or memantine alone or both donepezil and memantine or both galantamine and memantine). Another blood sample (approximately 4 mL) will be obtained at Visit 5 or ET for all subjects to measure lemborexant and its metabolites, as well as cognitive enhancers, as appropriate. (revised per Amendments 03 and 05)

For those subjects taking donepezil, the date and time of the 2 most recent doses of donepezil will be documented. For all subjects taking lemborexant, the date and time of the 2 most recent doses of lemborexant will also be documented. (revised per Amendment 03)

In case of early termination due to safety or any other reasons, a plasma sample for lemborexant (and its metabolites), and for any cognitive enhancer (as applicable) will be taken from the subject.

Pharmacodynamic Assessments

For modeling purposes, the change from baseline at the last week of treatment for the following efficacy variables aSE, aWE, SFI, WFI, IV, IS, AMP, and RA will be treated as PD variables.

Pharmacokinetic/Pharmacodynamic Assessments

For PK/PD assessments, the following efficacy variables aSE, aWE, SFI, WFI, IV, IS, AMP, and RA will be treated as PD variables.

Pharmacogenomic/Pharmacogenetic Assessments

Blood samples for genotyping and for additional exploratory analyses will be obtained at Baseline from consenting subjects.

Safety Assessments (revised per Amendment 05)

All subjects will undergo routine safety assessments at specified visits, including queries for AEs, ECGs, vital signs, weight, clinical hematology and chemistry analysis and urinalysis, and suicidality assessed using the eC-SSRS.

Safety assessments as listed above will be the only assessments conducted during the Extension Phase. (revised per Amendment 05)

Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. The electronic version of the questionnaire (ie, the eC-SSRS) will be completed by the subject with caregiver input. (revised per Amendment 05)

Morning Residual Effects

To assess morning residual effects, activity levels from the first 3 hours after waketime during the first 3 days of the first week of treatment and the same time interval during the last 3 days of treatment will be compared with the mean activity levels from the first 3 hours after waketime during the actigraphy baseline period. (revised per Amendment 05)

Other Assessments (revised per Amendment 05)

Cornell Scale for Depression in Dementia (CSDD)

The CSDD derives information from the patient and the informant (caregiver) to assess signs and symptoms of major depression in patients with dementia. Information is elicited through two semi-structured interviews; an interview with an informant and an interview with the patient, both of which focus on depressive symptoms and signs that occurred during the week preceding the interview. The final ratings of the CSDD items represent the rater's clinical impression rather than the responses of the informant or the patient. The CSDD, which takes approximately 20 minutes to administer, assesses a total of 19 items in the following 5 categories: mood-related signs, behavioral disturbance, physical signs, cyclic functions, and ideational disturbance. Each item within each category is rated for severity on a scale of 0-2 (0=absent, 1=mild or intermittent, 2=severe). The item scores are added. Scores above 18 indicate a definite major depression, scores above 10 indicate a probable major depression, and scores below 6 are associated with absence of significant depressive symptoms.

EuroQol 5 Dimensions – 5 Levels (EQ-5D-5L)

The EQ-5D-5L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on the patient's health status 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").

- The subject will self-complete the standard version of the EQ-5D-5L regarding his/her own status. The standard version is worded for self-completion, but is not labeled by EuroQol as the Self Version. For the purposes of this protocol and to differentiate from the Proxy version of the EQ-5D-5L, the standard version will be referred to as the Self Version.
    - For subjects with physical disabilities that impair self-completion (eg, arthritis or severe vision-impairment), caregivers or study coordinators may engage in assisted self-completion by reading questions and responses verbatim (without any interpretation) and/or recording responses for subjects as long as the responses are those of the subject.
- During the Core Study only, the caregiver will complete both the Self Version (regarding the caregiver) and the Proxy 1 Version (regarding the caregiver's perception of the subject). (revised per Amendment 05)
- Thus, 3 EQ-5D-5L forms per subject per visit should be completed: 1) subject Self Version, 2) caregiver Self Version, 3) caregiver Proxy 1 Version.

Zarit Burden Interview – short form (ZBI-short)

The ZBI-short was developed from the full ZBI, to be suitable for caregivers of cognitively impaired older adults across diagnostic groups. The ZBI-short can be used for cross-sectional, longitudinal, and intervention studies. It has been designed to reflect the stresses experienced by caregivers of dementia patients. The ZBI-short can be completed by caregivers directly or as part of an interview (eg, study coordinator interviews caregiver and completes based on caregiver response). Caregivers are asked

to respond to a series of 12 questions in 2 domains: personal strain and role strain. Each question is scored on a 5-point Likert scale from 0 to 4 (never to almost always). The range of summed scores is 0 to 48. Higher scores reflect a higher feeling of burden.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI will be used to assess the caregiver's quality of sleep. It is an instrument used to measure the quality and patterns of sleep in adults by measuring seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction, over the previous month. In scoring the PSQI, seven component scores are derived, each scored from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality. The PSQI will be administered to the caregiver, to assess his/her quality of sleep.

Bioanalytical Methods

Plasma concentrations of lemborexant and its metabolites (M4, M9, and M10), donepezil, memantine, and galantamine will be measured using validated liquid chromatography-tandem mass spectrometry assay methods. (revised per Amendment 03)

Statistical Methods

All statistical tests will be based on the 5% level of significance (two-sided), unless otherwise stated. No multiplicity adjustments will be made.

Study Endpoints (revised per Amendment 06)

Sleep-Related Endpoints (revised per Amendments 05 and 06)

The sleep-related endpoints are:

- The change from baseline of mean aSE during the last week of treatment with LEM compared to PBO (revised per Amendment 01)
- The change from baseline of aSE during each week of treatment with LEM compared to PBO. (revised per Amendment 06)
- Change from baseline in mean SFI during each week of treatment (revised per Amendments 01 and 06)
- Change from baseline of the mean duration of wake bouts (aMeanDurWB) over each week of treatment (revised per Amendments 01 and 06)

Wake-Related Endpoints (revised per Amendments 05 and 06)

- The change from baseline of mean aWE during each week of treatment with LEM compared to PBO (revised per Amendment 01)
- Change from baseline of the mean duration of sleep bouts (aMeanDurSB) over each week of treatment (revised per Amendments 01 and 06)
- Change from baseline of mean WFI during each week of treatment (revised per Amendments 01 and 06)

Circardian Rhythm-Related Endpoints (revised per Amendment 05 and 06)

- Change from baseline of IV, IS, L5, M10, AMP, and RA over each week of treatment (revised per Amendment 01)

Additional Endpoints (revised per Amendments 05 and 06)

The following endpoints will be analyzed for LEM2.5, LEM5, LEM10 and LEM15 compared to PBO:

- Safety and tolerability of LEM, including AEs and SAEs
- Change from baseline in CGIC-ISWRD Scale on symptoms of ISWRD total score and domains at Day 29 (revised per Amendments 01 and 06)
- Change from baseline of the sum of activity counts and change from baseline of the number of bouts >10 minutes of sleep in the first 3 hours after morning waketime on the first 3 days and last 3 days of treatment
- Rebound sleep and wake fragmentation endpoints as assessed from actigraphy during the Follow-Up Period
  - Change from baseline in mean aSE of the first 7 nights, and aSE of the second 7 nights of the Follow-up Period
  - Change from baseline in mean aWE of the first 7 days and mean aWE of the second 7 days of the Follow-Up Period
  - Proportion of subjects whose mean aSE is higher than at baseline for the first 7 nights or the second 7 nights of the Follow-Up Period
  - Proportion of subjects whose mean aWE is longer than at baseline for the first 7 days or the second 7 days of the Follow-Up Period (revised per Amendment 03)
- Change from baseline on ADAS-cog at Day 29
- Change from baseline on MMSE at Day 29
- Change from baseline sleep quality in caregivers as measured by the PSQI at Day 29
- Change from baseline of caregiver burden on on all scores of the ZBI-short form at Day 29. (revised per Amendment 06)
- Change from baseline on the EQ-5D-5L utility and Visual Analogue Scale (VAS) scores at Day 29 for both subject and caregiver
- Change from baseline of the total score of NPI-10 at Day 29
- Change from baseline on SDI at Day 29
- Characterize the PK of lemborexant using the population approach and descriptive statistics for the plasma concentrations of its metabolites M4, M9, and M10. (revised per Amendment 06)
- Relationships between exposure to lemborexant, efficacy, and/or safety variables using PK/PD modeling
- Plasma concentration of lemborexant and any cognitive enhancer(s) in subjects taking both drugs
- Evaluate the long-term safety and tolerability of flexible doses of LEM5, LEM10, and LEM15 per day over a period of 30 months in subjects with ISWRD who have completed the Core Study. (revised per Amendments 05 and 06)

Analysis Sets

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

The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of

randomized study drug and had at least 1 postdose efficacy measurement.

The PK Analysis Set is the group of subjects who have at least 1 quantifiable plasma concentration of lemborexant, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least 1 quantifiable lemborexant concentration data point as per the PK Analysis Set.

Core Study (revised per Amendment 05)

Efficacy Analyses

Analysis for the Sleep-Related, Wake-Related, and Circadian Rhythm-Related Endpoints (revised per Amendment 06)

The change from baseline of the mean aSE for the last week and for each week on treatment, and the change from baseline of mean aWE for the last week on treatment will be analyzed using MCP-MOD (Multiple Comparisons & Modelling) approach. Dose response models that will be evaluated are linear, linear log, quadratic, exponential, e_{max}, sigmoid e_{max}, beta and logistic. (revised per Amendments 05 and 06)

Analysis stage – MCP-step: Establish a dose-response signal (the dose-response curve is not flat) using multiple comparison procedure. Based on the observed data, the model that shows statistically significant trend test will be selected (at one-sided 5% significance). If more than one is statistically significant, then the most optimal model using Akaike Information Criteria will be selected. This method prospectively controls the type I error at 5%.

Analysis Stage – Mod-step: Dose response and target dose estimation will be based on dose response modelling. MCP-MOD approach allows for interpolation between doses.

As a sensitivity analysis to the aSE and aWE endpoints, the mean aSE and mean aWE for Week 4 will be analyzed using the longitudinal data analysis (LDA). (revised per Amendments 01 and 06)

The change from baseline of the following endpoints will be analyzed using LDA on the FAS for LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, as appropriate: mean SFI, mean WFI, mean aMeanDurWB, mean aMeanDurSB, IV, IS, L5, M10, AMP, and RA . (revised per Amendment 06) The model will include all data and will be adjusted for the corresponding baseline value, country, treatment, time (Week 1, Week 2, Week 3 and Week 4) and the interaction of treatment by time. Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The LDA model accounts for any missing data, and assumes that the missing data are missing at random. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. Where data are normally distributed, least square (LS) means, difference in LS means of each lemborexant dose compared to PBO, 95% confidence intervals (CIs) and P values at the appropriate time point will be presented. (revised per Amendment 01)

Additional analyses as deemed necessary, may include the investigation of subgroup analyses and/or addition of covariates to the model of age, sex, race, body mass index (BMI), severity of aSE, severity of aWE, wake fragmentation, severity of AD-D based on MMSE and/or other subgroups. (revised per Amendment 06)

Analyses for Additional Endpoints (revised per Amendment 06)

The overall score of CGIC-ISWRD Scale at Day 29 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusted for country. (revised per Amendment 01)

To assess residual morning sleepiness levels, change from baseline in the sum of activity counts in the 3 hour interval after morning waketime will be compared for each treatment group relative to placebo for each of the 6 mornings comprising the first 3 days and last 3 days of treatment. The change from baseline will be analyzed using analysis of covariance (ANCOVA), with treatment and baseline as fixed effects. Provided that the data are normally distributed, LS means, difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% CIs, and p--values will be presented. In addition, the change from baseline of the number of bouts >10 min scored as sleep will be determined. The change from baseline will be analyzed using ANCOVA, as above.

Rebound sleep and wake fragmentation are defined as worsened aSE or aWE compared to baseline after study drug treatment is completed. Actigraphy data from the Follow-Up Period will be compared to actigraphy data from the baseline to assess whether subjects experience rebound sleep or wake fragmentation. Specifically, a lower value for aSE or aWE during the Follow-Up Period compared to the mean aSE or aWE value during baseline will be considered worsened sleep or wake fragmentation.

To assess rebound sleep and wake fragmentation, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the 2 weeks of the Follow-Up Period the proportion of subjects whose corresponding value for aSE or aWE exceeds the corresponding baseline value by 1% for aSE and 0.5% for aWE (which is approximately 5 minutes based on the total length of each assessment period) 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.

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for country and treatment. The LS mean of each week of the Follow-Up Period will be compared to the baseline between each treatment group and placebo. If the upper bound of the 95% CI of aSE or aWE for the mean of each week of the Follow-Up Period is less than the lower bound of a 95% CI for the values during the baseline in the given treatment group, it will be considered strong evidence for rebound sleep or wake fragmentation. If the LS means for aSE and aWE for the Follow-Up Period are all higher than for the baseline, then no rebound sleep or wake fragmentation 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 sleep and/or wake fragmentation is present.

Each domain of CGIC-ISWRD Scale at Day 29 will be analyzed using the Cochran–Mantel–Haenszel test, adjusted for country. (revised per Amendment 01)

The change from baseline of total score from the NPI-10, SDI, ADAS-Cog and MMSE at Day 29 will be analyzed with ANCOVA, with treatment and baseline as fixed effects on the Efficacy Analysis Set. The difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% CIs and *P*-values will be presented. (revised per Amendment 05)

Pharmacokinetic Analysis

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

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK data from this study will be pooled with relevant data from existing Phase 1 and 2 studies, and other Phase 3 studies if available. The effect of intrinsic and extrinsic factors (ie, demographics, concomitant medications) on the PK of lemborexant will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and volume of distribution (V/F). Derived exposure

parameters such as area under the concentration-time curve (AUC), maximum observed plasma concentration (C_{max}) and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL/F and dosing history. (revised per Amendment 05)

Baseline plasma concentrations of cognitive enhancer(s) from appropriate subjects will be compared to those at end of treatment. Plasma concentrations taken at the end of study will be compared to corresponding baseline concentrations to assess for evidence of potential drug-drug interaction. (revised per Amendment 03)

Pharmacodynamic Analysis

All of the PD variables are considered efficacy variables for the purposes of analysis. (revised per Amendment 01)

Pharmacogenomic Analyses

DNA samples will be collected and stored, and may be used to examine the role of genetic variability in absorption, distribution, metabolism, and excretion, or development of AEs. Variation in lemborexant exposure or AEs may be explored by correlation of single-nucleotide polymorphisms with PK, safety, or efficacy data. Efficacy will be explored in relation to APOε4 genotype.

Pharmacokinetic/Efficacy Analyses

The PK/Efficacy relationship between exposure to lemborexant and efficacy variables including but not limited to SFI and WFI, and the most frequently occurring TEAEs, will be explored graphically. Any emergent PK/Efficacy relationships will be evaluated by population PK/Efficacy modeling. The population PK/Efficacy analysis plan will be described and results will be reported in a separate document.

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

Safety Analyses

Evaluations of safety will be performed on the relevant Safety Analysis Set. The incidence of AEs and suicidality (eC-SSRS), along with change from baseline in laboratory safety test variables, ECGs, vital sign and weight measurements, will be summarized by treatment group using descriptive statistics.

In addition to typical events associated with special situations (EASSs), designated compound-specific EASSs will be summarized separately. These will include Customized MedDRA Queries for AEs that could potentially be considered cataplexy or seizure. (revised per Amendment 02)

Other Analyses

Endpoints may also be presented graphically or analyzed by modeling methods if warranted. (revised per Amendment 06)

The change from baseline of the EQ-5D-5L utility and VAS scores, the global score of PSQI, all scores of the ZBI-short and the SDI at Day 29 will be analyzed using ANCOVA, with treatment and baseline as fixed effects. Provided that the data are normally distributed, LS means, difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% confidence intervals (CIs) and p-values will be presented. The analyses for the EQ-5D-5L (caregiver self-version), PSQI, and ZBI will be conducted for a) caregivers who reside in the same residence as the subjects, b) caregiver informants who do not, reside in the same residence as the subjects, and c) all types of caregivers/informants combined. (revised per Amendment 01)

Extension Phase (revised per Amendment 05)

Efficacy

The change from baseline of scale domains, as well as total score from the efficacy endpoint SDI will be summarized by time point and by modal dose.

Other comparisons may be performed as deemed appropriate in the future (subjects who remain on LEM10 and never switch vs subjects who switched from LEM10), and these will be included in the Extension Phase SAP.

Safety Analysis

The analysis of safety data will be performed by time point and modal dose. Other comparisons may be performed if appropriate; these will be included in the SAP.

The safety endpoints of adverse events (TEAEs, SAEs, and AEs leading to discontinuation) will be summarized by System Organ Class (SOC) and Preferred Term (PT), and the incidence of AEs will be summarized by maximum severity and relationship to study drug. Change from baseline analyses will be presented for clinical laboratory values, vital signs and weight, ECGs, and physical examination results. The results of eC-SSRS assessments will be listed for each subject, and the incidence of treatment-emergent suicidal ideation or suicidal behavior will be summarized by treatment group using descriptive statistics.

Interim Analyses

A database lock will occur after all of the subjects have completed the Core Study, including the End of Study visit. The Core Study data will be analyzed according to the Core Study statistical analysis plan (SAP). A second database lock will occur after the End of Study visits have been completed for the Extension Phase. Analyses for the Extension Phase will be based on the Extension Phase SAP.

An interim analysis will be conducted with only the subjects from the US and Japan; details will be provided in the SAP. (revised per Amendments 05 and 06)

Sample Size Rationale

Approximately 60 subjects will enroll in this proof-of-concept study. (revised per Amendment 06)

Some supporting exploratory power estimation is based on testing the dose response using the MCP-Mod package in R; several dose response curves were explored at one-sided 0.05 level of significance with different values of n (12, 13, and 14 subjects) per treatment group. (revised per Amendment 06)

Conservative scenarios based on 10 percentage point difference between the active drug and placebo will be presented. (revised per Amendment 06)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AD	Alzheimer's Disease
AD-D	Alzheimer's Disease -- Dementia
AE	adverse event
AHI	apnea-hypopnea index
aMeanDurSB	Mean duration of sleep bouts > 10 min during the defined wake period
aMeanDurWB	Mean duration of wake bouts > 10 min during the defined sleep period
AMP	amplitude of the rest-activity rhythm
ANCOVA	analysis of covariance
aSE	actigraphy sleep efficiency
AUC	area under the concentration-time curve
aWE	actigraphy wake efficiency
BMI	body mass index
BP	blood pressure
CA	Competent Authority
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
CSDD	Cornell Scale for Depression in Dementia
CSF	cerebrospinal fluid
CT	computed tomography
DORA	dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th edition
EASS	events associated with special situations
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia–Suicide Severity Rating Scale
EOS	end of study
EQ-5D-5L	Euro-QOL version 5 dimensions, 5 levels

Abbreviation	Term
ET	Early Termination
EU	European Union
FAS	full analysis set
FI	fragmentation index
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H	high
CGIC-ISWRD Scale	Clinician's Global Impression of Change -Irregular Sleep-Wake Rhythm Disorder Clinical Assessment Scale
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	intradaily variability
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	interdaily stability
ISWRD	Irregular Sleep-Wake Rhythm Disorder
KSS	Karolinska Sleepiness Scale
L	low
LDA	longitudinal data analysis
LEM	lemborexant
LEM2.5	lemborexant, 2.5 mg dose
LEM5	lemborexant 5 mg dose
LEM10	lemborexant, 10 mg dose
LEM15	lemborexant, 15 mg dose
LNH	low-normal-high
LS	least square
MCB	median calculated bedtime
MedDRA	Medical Dictionary for Regulatory Activities
MI	movement index
MMSE	Mini Mental State Examination
M-MSLT	Modified Multiple Sleep Latency Test

Abbreviation	Term
N	normal
NPI-10	Neuropsychiatric Inventory – 10 item version
OSA	obstructive sleep apnea
PBO	placebo
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
PSG	polysomnography
PSG SE	polysomnography sleep efficiency
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
QT	period from the beginning of the QRS complex to the end of the T wave on an electrocardiogram.
QTcF	QT corrected for heart rate using Fridericia's formula
RA	relative amplitude
REM	rapid eye movement
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDI	Sleep Disorders Inventory
SDLP	standard deviation of lateral position
SE	Sleep Efficiency
SFI	Sleep Fragmentation Index
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
TIB	time in bed
TOB	time out of bed
US	United States
VAS	Visual Analogue Scale
V/F	apparent volume of distribution
WFI	Wake Fragmentation Index
ZBI	Zarit Burden Inventory
ZOP	Zopiclone

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent forms (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 Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations including Federal Regulations, Title 21, Code of Federal Regulations (CFR) Part 56. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates (CRA[s]), change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

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

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

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA 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 Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (Committee for Medicinal Products for Human Use/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of United States 21 CFR Part 312
- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states (revised per Amendment 04)
- 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

5.3 Subject Information and Informed Consent

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

At the Screening Visit, this informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or caregiver (or, if applicable, the legally authorized representative) should understand the statements before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if the caregiver (or, if applicable, the legally authorized representative) is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICFs and any other written information to be provided to subjects are read and explained to the subject or the caregiver (or, if applicable, the legally authorized representative), and after the subject or the caregiver (or, if applicable, the legally authorized representative) has orally consented to the subject's participation in the study and, if capable of doing so, has signed

and personally dated the ICFs, the witness should sign and personally date the consent forms. The subject will be asked to sign the ICFs before any study-specific procedures are performed. No subject can enter the study before his/her informed consents have been obtained.

Unsigned copies of IRB/IEC-approved ICFs must be prepared in accordance with ICH E6, Section 4, and Federal Regulations, Title 21 CFR Part 50. Each subject and caregiver must sign the approved ICFs before study participation. The forms must be signed and dated by the appropriate parties. The original, signed ICFs for each subject and caregiver (and, if applicable, the legally authorized representative) will be verified by the sponsor and kept on file according to local procedures at the site.

The subject and caregiver (and, if applicable, the legally authorized representative) should be informed in a timely manner if new information becomes available that may be relevant to the subject's and caregiver'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 60 investigational sites in the United States (US), European Union (EU), and Japan. (revised per Amendments 01 and 04)

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

7 INTRODUCTION

7.1 Indication

7.1.1 Irregular Sleep-Wake Rhythm Disorder in Alzheimer's Disease Dementia

Sleep disturbances appear early in the course of Alzheimer's Disease – Dementia (AD-D) and other dementias and are associated generally with a loss of circadian rhythmicity (Guarnieri and Sorbi, 2015; Musiek et al., 2015). Patients with AD-D and other dementias can spend much of the night awake, and much of the daytime hours asleep. When sleep is not consolidated at night but rather distributed in sleep bouts across the 24-hour day, this pattern is referred to as Irregular Sleep-Wake Rhythm Disorder (ISWRD) (Figure 1). This disorder is characterized by decreased amplitudes of the sleep-wake and alertness rhythms, with less predictability of the sleep-wake pattern from day to day (Satlin et al., 1995; Peter-Derex et al., 2015).

The ISWRD pattern can be visualized in Figure 1 this irregular sleep-wake rhythm is frequently seen in association with neurologic dysfunction, including AD-D (Abbott and Zee, 2015). Since actigraphy can capture the full 24-hour pattern of sleep and wake in treatment trials, actigraphy has been a common choice (Camargos et al., 2013). Using data on activity counts collected with an accelerometer device, with support from sleep log data, algorithms can be applied to define intervals of sleep and wake across the 24-hour day, as well as within the sleep log-defined night/in-bed interval and day/out-of-bed interval. This noninvasive methodology allows for continuous observation from which objective efficacy variables may be derived (Goncalves et al., 2014). In the top panel of Figure 1, the healthy control subject shows high levels of activity across the day, quiescent nighttime sleep periods, and interdaily stability. By contrast, the data in the lower panel of Figure 1 show the reduced amplitude and irregularity of the sleep-wake pattern in a subject with AD-D (Satlin et al., 1992).

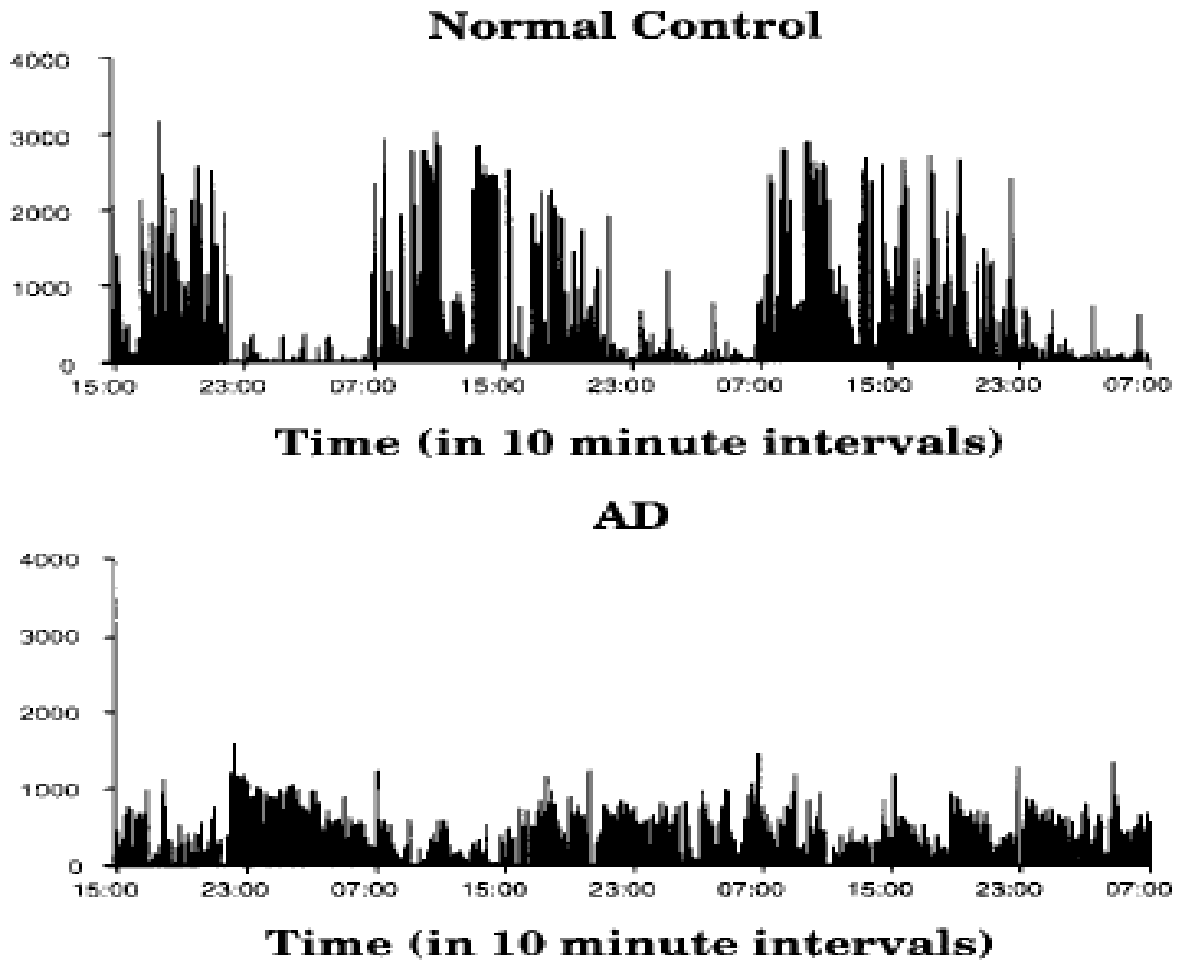

Figure 1 Representative Activity Data Graphs for a Normal Control and a Subject with Alzheimer's Disease (AD)

Sleepiness during the day can substantially impact quality of life for the patient with dementia (Carvalho-Bos et al., 2007). While the importance of sleep problems in the development, progression, management, and treatment of dementia is still not fully recognized, sleep-wake disturbances are a highly prevalent and often disabling feature of AD-D (Miller, 2015). Research has shown that the inability to sleep at night is among the leading causes of institutionalization (Pollak and Perlik, 1991), since wakefulness during the night not only poses a safety risk to the patient, eg, by increasing the risk of wandering or falling in the dark, but also increases the burden on caregivers whose sleep is also disrupted.

ISWRD, (International Classification of Diseases [ICD]-10 code G47.23) is also listed in Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5), and is diagnostically distinct from insomnia. Relative to healthy, age-matched subjects, nocturnal sleep in patients with AD-D is disrupted by fragmentation. With many awakenings shorter than 10 minutes and a few longer bouts of wakefulness, this results in substantially lower sleep efficiency and unrefreshing sleep (Liguori et al., 2016). Patients with AD-D also have difficulty maintaining wakefulness throughout the daytime hours, and report excessive daytime sleepiness. This contrasts with insomnia disorder, in which patients may have difficulties with initiating and/or maintaining sleep during the nocturnal sleep period, but do not exhibit symptoms of excessive daytime sleepiness and have difficulty napping during the day (Pillai et al., 2016). In addition, when patients with AD-D awaken at night, they are at risk for confusion and falls in association with the awakenings whereas aberrant nocturnal behaviors are generally not associated with middle-of-the-night awakenings in insomnia disorder, except in association with the uses of some types of hypnotic medications.

Figure 2 is a schematic of ISWRD as defined by actigraphy, demonstrating a typical pattern of fragmentation (Campbell et al., 1999).

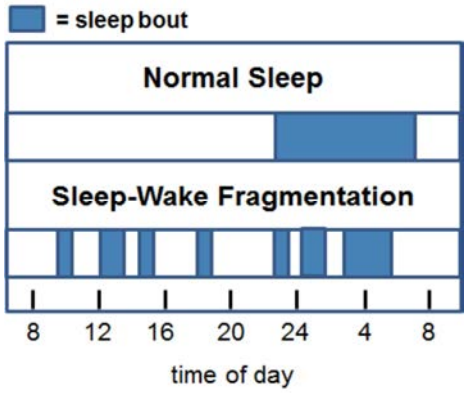

Figure 2 Schematic Activity Data Graphs for Normal Sleep and Fragmented Sleep (revised per Amendment 01)

7.1.2 Unmet Medical Need

While medications are often prescribed to treat sleep difficulties in this patient population, there are currently no treatments approved to treat ISWRD. Benzodiazepine and non-benzodiazepine sedative hypnotics can cause confusion, increase cognitive impairment, slow reaction, and worsen balance, leading to falls (National Institute of Aging AD treatment guide). Drugs in this class can especially predispose to confusion and falls during middle-of-the-night awakening (FDA Questions and Answers: Risk of next-morning impairment after use of insomnia drugs, 2014). Sedating antidepressants such as trazodone, and antihistamines with anticholinergic properties, can potentially exacerbate cognitive difficulties, sleepiness, and confusion (Peron et al., 2011). Typical and atypical antipsychotics are associated with increased risk of death in elderly dementia patients, which resulted in a black-box warning for these drugs, and can also cause sedation, confusion, and Parkinsonian symptoms (FDA Information for Healthcare Professionals: Conventional Antipsychotics, 2008). A recent guideline (Auger et al., 2015) recommends the avoidance of currently available sleep aids including melatonin to treat sleep disturbances in patients with dementia. Thus, there is an unmet medical need for an effective and safe alternative to drugs that are currently used off-label and carry risks (Salami et al., 2011).

7.1.3 Rationale for a Dual Orexin Receptor Antagonist to Treat Irregular Sleep-Wake Rhythm Disorder

The orexin neurotransmitter system is directly involved in modulation of the circadian sleep-wake rhythm, with orexins promoting wakefulness. In populations with Mild Cognitive Impairment (Liguori et al., 2016) and mild to severe AD (Liguori et al., 2014), elevated orexin levels have been associated with both disturbed sleep and impaired cognition. In human studies, disrupted sleep was associated with more severe cognitive impairment (lower scores on the Mini Mental State Examination [MMSE]) and with higher orexin levels in cerebrospinal fluid (CSF). These higher CSF orexin levels were correlated with higher tau protein levels in CSF. In addition, in these studies, rapid eye movement (REM) sleep was shown to be decreased in subjects with higher orexin levels. As noted, REM sleep is involved in memory function.

Thus, lemborexant, a DORA that will block an over-active orexin system, has the potential not only to improve sleep, but to impact the underlying neuropathology.

7.1.4 Clinical Experience with Lemborexant

7.1.4.1 Phase 1

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

E2006-A001-002 (Study 002): Multiple ascending dose study. This study enrolled healthy adult and elderly subjects, each of whom was dosed with lemborexant or placebo at night. In

addition to determining the safety and tolerability of multiple doses, the study also provided preliminary evidence of a lack of important differences in exposure between adult and elderly subjects.

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

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

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

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

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

E2006-A001-012 (Study 012): Drug-drug interaction study. These study results demonstrated that: (1) coadministration of a moderate CYP3A inhibitor (fluconazole) showed a moderate interaction as demonstrated by a 1.63-fold increase in C_{max} and 4.2-fold increase in AUC of lemborexant; (2) coadministration of lemborexant had no statistically significant effect on oral contraceptives (ethinyl estradiol and norethindrone), which also did not alter the PK of lemborexant; and (3) concomitant administration of a gastric acid suppressant agent had a weak interaction as shown by a 27% decrease in C_{max} and no impact on AUC of lemborexant. (revised per Amendment 06)

E2006-E044-106 (Study 106) was a randomized, double-blind, placebo-controlled, 4-way incomplete block crossover study in healthy volunteers to evaluate on-road driving safety. The primary objective was to demonstrate that lemborexant 2.5, 5, and 10 mg compared to placebo (PBO) does not impair driving as assessed by standard deviation of lateral position (SDLP) during an on-road driving test in the morning following a single dose (Day 2) and multiple doses (Day 9) of lemborexant administered at bedtime. An active comparator, zopiclone 7.5 mg (ZOP) was included for assay sensitivity. All subjects received placebo and

zopiclone, and 2 of the 3 lemborexant doses. A total of 48 subjects were randomized and completed all 4 treatment periods; no subject discontinued from the study. No drives were stopped or never started while subjects were taking lemborexant; 3 drives from 2 subjects were stopped when subjects were taking ZOP. The primary objective was met, ie, for drives on both Day 2 and Day 9, for all lemborexant doses, the upper bound of the 95% CI for SDLP treatment difference from PBO did not exceed the prespecified clinically meaningful threshold of 2.4 cm. Symmetry analyses were not statistically significant for any lemborexant dose at either Day 2 or Day 9, indicating that the frequency of subjects with SDLP treatment difference from PBO ≥2.4 cm (impaired) was similar to the frequency of subjects with SDLP treatment difference from PBO ≤–2.4 cm (improved). Assay sensitivity was demonstrated: for ZOP, the upper bound of the 95% CI of SDLP treatment difference from PBO exceeded 2.4 cm (Days 2 and 9), and the symmetry analyses for ZOP were statistically significant (Days 2 and 9). (revised per Amendment 05)

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

7.1.4.2 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 and wake after sleep onset. These changes were largely maintained over 15 days of treatment with lemborexant as compared with placebo. Subjective measures derived from sleep diary entries yielded results largely comparable to PSG-derived results. Further, there was no evidence of rebound insomnia after treatment was completed, as measured either by PSG or sleep diary.

At doses up to 10 mg, changes from baseline in next-day sleepiness, as measured by the KSS, did not differ from those after placebo. At the highest doses of 15 and 25 mg, the

increase in KSS from baseline was statistically significantly different from placebo at some time points, but the increases in KSS were of small magnitude (ie, less than 1 unit on average). Although there was approximately a one- to two-fold accumulation of lemborexant in plasma over the 15-day Treatment Period across the dose range, next-day sleepiness did not increase from the beginning to the end of treatment.

7.1.4.3 Summary of Clinical Experience

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.

At the doses (2.5/5/10 mg) currently being studied for the treatment of insomnia disorder, lemborexant has been well-tolerated. In the Phase 2 study (E2006-G000-201 [Study 201]), lemborexant had no significant impact on morning cognitive performance tasks. Lemborexant was shown to improve sleep latency and sleep maintenance, both objectively by PSG and subjectively via daily sleep diaries. In addition, lemborexant increases total sleep time, including REM sleep, which may help to improve or stabilize memory function.

Safety and efficacy findings in elderly subjects with insomnia were not different from those in younger subjects. There are no important exposure differences between males and females or between older and younger individuals. Lemborexant is metabolized by CYP3A4. Although donepezil and galantamine are also metabolized by CYP3A4, the likelihood of interaction with lemborexant is low as lemborexant is not a CYP3A inhibitor. Memantine is metabolized by pathways not involving CYP3A4. Therefore, the drugs typically administered for amelioration of dementia are not expected to have any clinically relevant metabolic interactions with lemborexant. However, an analysis will be conducted to identify any potential PK interactions between lemborexant and these drugs. (revised per Amendment 03)

In general, E2006 does not impact CYP3A substrates but has a mild effect on CYP2B6 substrates. Co-administration with a moderate inhibitor of CYP3A (fluconazole) and a strong inhibitor of CYP3A (itraconazole) increased plasma concentration whereas the exposure was greatly reduced by a strong CYP3A inducer (rifampin). Therefore, moderate and strong inhibitors and strong inducers are prohibited. Following the ingestion of a high-fat breakfast, a mild food effect was noted in the fed condition of a standard food effect study. Lemborexant should not be consumed within a few hours of a meal. (revised per Amendment 06)

7.1.5 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

The present study will evaluate the effects of daily lemborexant doses for 4 weeks in subjects with mild or moderate AD-D who complain of disrupted sleep or multiple awakenings at night along with frequent periods of falling asleep during the day that impacts the quality of life of the subject. In addition to actigraphy, a battery of psychometric assessments will be administered to evaluate effects on well-being of both the subject and the caregiver. The use of these measures in this subject population during administration of lemborexant should lead to a better understanding of the therapeutic potential of lemborexant in ISWRD.

8 STUDY OBJECTIVES

8.1 Sleep-Related Objectives (Revised per Amendments 05 and 06)

- To determine the dose response of lemborexant 2.5 mg (LEM2.5), 5 mg (LEM5), 10 mg (LEM10) and 15 mg (LEM15) compared to placebo (PBO) on the change from baseline in actigraphy-derived Sleep Efficiency (aSE) during the last week of treatment in subjects with Alzheimer's disease dementia (AD-D) who have ISWRD. (revised per Amendments 01, 05, and 06)
- To determine the efficacy of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO on the change from baseline aSE during each week of treatment. (revised per Amendment 06)
- To determine the efficacy of lemborexant LEM2.5, LEM5, LEM10 and LEM15 compared to PBO on the change from baseline on the Sleep Fragmentation Index (SFI) during each week of treatment. (revised per Amendment 06)To determine the change from baseline of the mean duration of wake bouts (aMeanDurWB) over each week of treatment. (revised per Amendment 06)

8.2 Wake-Related Objectives (revised per Amendments 05 and 06)

- To determine the dose response of lemborexant 2.5 mg (LEM2.5), 5 mg (LEM5), 10 mg (LEM10) and 15 mg (LEM15) compared to placebo (PBO) on the change from baseline in actigraphy-derived Wake Efficiency (aWE) during the last week of treatment in subjects with Alzheimer's disease dementia (AD-D) who have ISWRD. (revised per Amendments 01, 05, and 06)
- To determine the efficacy of lemborexant LEM2.5, (LEM5, LEM10, and LEM15 compared to PBO on the change from baseline of actigraphy-derived Wake Efficiency (aWE) during each week of treatment. (revised per Amendment 06)
- To determine the efficacy of lemborexant LEM2.5, LEM5, LEM10, and LEM15 compared to PBO on the change from baseline of the Wake Fragmentation Index (WFI) during each week of treatment. (revised per Amendments 01 and 06)
- To determine the change from baseline of the mean duration of sleep bouts (aMeanDurSB) over each week of treatment. (revised per Amendment 06)

8.3 Circadian Rhythm-Related Objectives (revised per Amendments 05 and 06)

- To evaluate onset and treatment course effect as measured by change from baseline of intradaily variability (IV), interdaily stability (IS), amplitude of the rest-activity rhythm (AMP), relative amplitude of the rest-activity rhythm (RA), and other actigraphy variables during each week of treatment. (revised per Amendment 06)

8.4 Additional Objectives (revised per Amendment 05 and 06)

- To evaluate the safety and tolerability of lemborexant.
- To explore the effects of LEM2.5, LEM5, LEM10, LEM15, and PBO at the end of 4 weeks of treatment (unless otherwise specified)` on the following:
  - Change from baseline of sum of activity counts and change from baseline of the number of bouts >10 minutes of sleep in the first 3 hours after morning waketime on each of the first 3 days and last 3 days of treatment as an indicator of next-morning residual effects.
  - Potential rebound ISWRD in the 2 weeks following 4 weeks of treatment.
  - Onset and course of treatment effect as measured by change from baseline of Clinician's Global Impression of Change-ISWRD (CGIC-ISWRD) Scale on symptoms of ISWRD total score and domains. (revised per Amendments 01 and 06)
  - Change from baseline of Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog).
  - Change from baseline in Mini Mental State Examination (MMSE).
  - Change from baseline in sleep quality in caregivers as measured by the Pittsburgh Sleep Quality Index (PSQI).
  - Change from baseline of caregiver burden on the Zarit Burden Interview – short form (ZBI).
  - Change from baseline of Health outcomes of the subject and/or caregiver on the EuroQOL version 5D-5L (EQ-5D-5L) (subject Self Version, caregiver Self Version, caregiver Proxy 1 Version).
  - Change from baseline of Mood and behavior on the Neuropsychiatric Inventory (NPI-10; by caregiver as proxy for the subject).
  - To characterize the pharmacokinetics (PK) of lemborexant using the population approach.
  - To explore the PK/pharmacodynamic (PD) relationship between exposure to lemborexant and selected efficacy variables and most frequently occurring treatment-emergent adverse events (TEAEs).
  - To assess the plasma concentrations of cognitive enhancers (cholinesterase inhibitors and/or memantine) and lemborexant in subjects taking such drugs.

- To evaluate the long-term safety and tolerability of flexible doses of LEM5, LEM10, and LEM15 per day over a period of 30 months in subjects with ISWRD who have completed the Core Study (revised per Amendments 05 and 06).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E2006-G000-202 is a multicenter, randomized, double-blind, PBO-controlled, parallel-group study of 4 doses of lemborexant or PBO taken daily for 4 weeks in approximately 60 male or female subjects, ages 60 to 90 years, with mild or moderate AD-D who complain of disrupted sleep or multiple awakenings at night along with frequent periods of falling asleep during the day that impacts the quality of life of the subject. For each subject, an individual who knows the subject well and will provide the information about themselves will also be enrolled in the study (see Caregivers and Informants, below). Additional informants may also be associated with the study but will not be required to complete a consent form. (revised per Amendments 01 and 06)

The study will have 3 phases: the Prerandomization Phase, the Randomization Phase, and the Extension Phase (Figure 3). The Prerandomization Phase will comprise 2 periods that will last up to a maximum of 42 days: a Screening Period and a Baseline Period. The Randomization Phase will comprise a Treatment Period during which subjects will be treated for 4 weeks, and a minimum 14-day Follow-Up Period before an End of Study visit. The Extension Phase comprises a 30-month Maintenance Period and a 14-day Follow-Up Period. Subjects who complete the Core Study End of Study (EOS) Visit within 30 days prior to enrollment in the Extension Phase will be eligible for participation. For subjects continuing directly from the Core Study into the Extension Phase, the EOS Visit of the Core Study will be the start of the Extension Phase. Subjects who complete the Core Study, but who do not elect to immediately continue into the Extension Phase have up to 30 days after the EOS Visit to participate. These subjects will be required to return to the site within 30 days of completion of the EOS Visit to repeat selected assessments before being dispensed drug for the Extension Phase. (revised per Amendments 03 and 05)

Throughout the Prerandomization Phase and the Randomization Phase, all subjects will undergo routine safety assessments at specified visits, including questioning regarding AEs; suicidality; 12-lead electrocardiograms (ECGs); vital signs, weight; clinical hematology and chemistry analysis; and urinalysis. (revised per Amendment 01)

Subjects will not be excluded if they attend adult day care as long as the day care staff can ensure that the actigraph remains on the subject's wrist and, if removed, is returned as promptly as possible, with notation of the replacement noted for the informant to include on the sleep log. (revised per Amendment 01)

9.1.1 Caregivers and Informants (revised per Amendment 01)

For the subject to enroll, there must be 1 or more persons who can provide the required information for assessments, complete the sleep log for actigraphy, and ensure that the subject is dosed at the appropriate time. These roles can be fulfilled by the same or different individuals. For each subject, one individual will be designated as the "caregiver informant" (or "caregiver"), who will be sufficiently familiar with the subject to provide information to the site staff with respect to the subject's sleep and wake patterns, behavior, mood, AEs, and

quality of life. Typically, the caregiver informant will need to spend at least 10 hours per week with the subject. (revised per Amendment 01)

If the caregiver informant does not reside with the patient, then the other informant(s) will be responsible for ensuring that the sleep log is completed daily and that dosing occurs at the appropriate time. There can be more than one such informant, as in the case of home health aides who stay with the subject during the week and change on the weekend. (revised per Amendment 01)

If the individual who is originally designated as the caregiver informant cannot fulfill the function, he/she may be replaced by a suitable alternate until the Baseline Visit, and thereafter only following consultation with the Sponsor. (revised per Amendment 01)

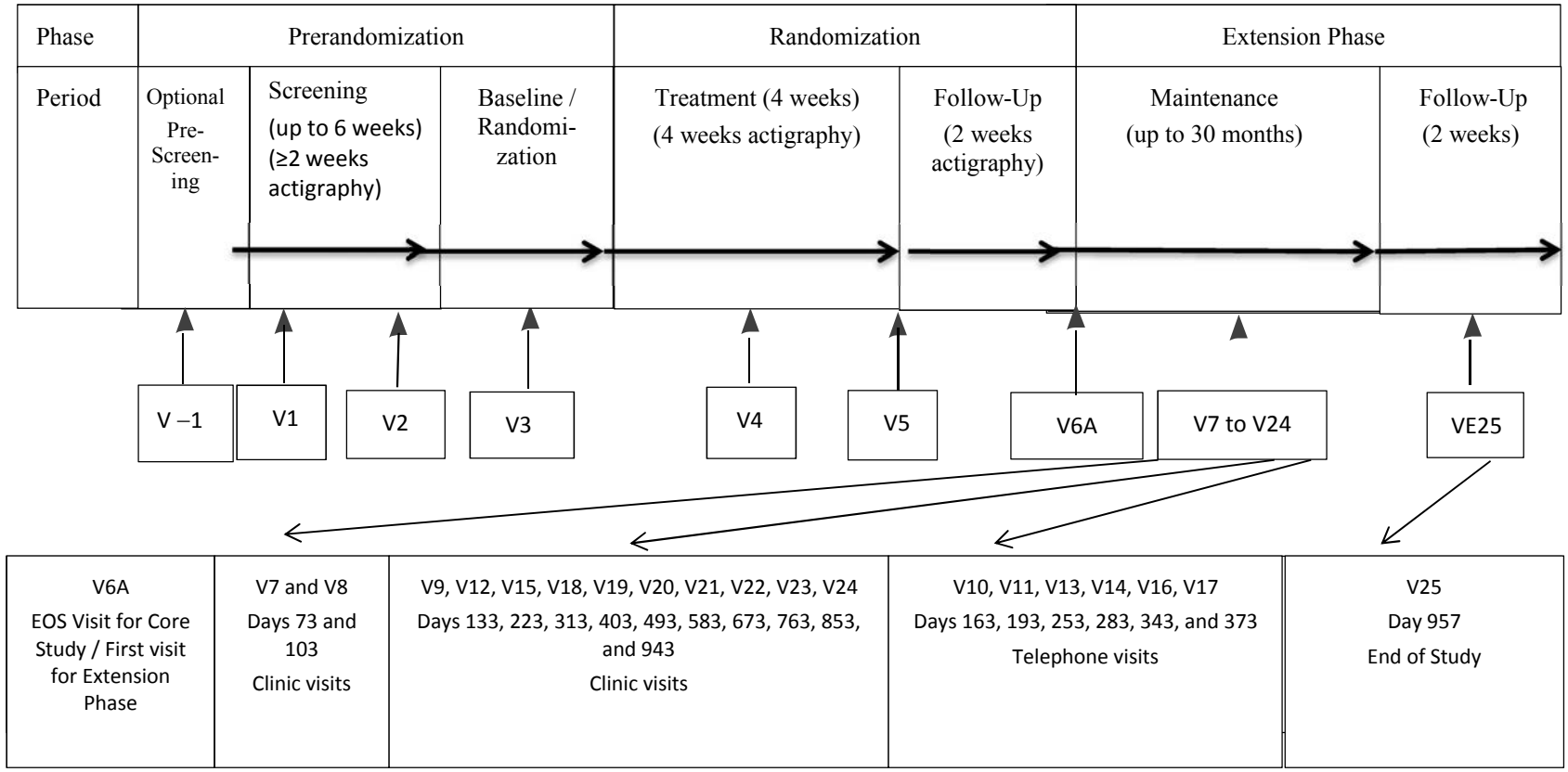

Figure 3 Study Design (revised per Amendments 03 and 05)

Note: Visit –1 is an optional Prescreening Period for subjects and caregivers who are unsure whether the subject has Irregular Sleep-Wake Rhythm Disorder (ISWRD). Subjects will wear an activity tracker for approximately 4 days, then return to the site to have the data from the activity tracker downloaded and analyzed to determine whether they are candidates for the study. (revised per Amendment 05)

Note: Visit 2 is a caregiver visit for downloading actigraphy data to determine eligibility; Visit 3 is the baseline visit for both subject and caregiver; Visit 4 is a visit for both subject and caregiver to download actigraphy data and perform safety assessments; Visit 5 is the end-of-treatment assessments visit; and Visit 6A is for end-of-study assessments for the Core Study. For subjects continuing directly from the Core Study into the Extension Phase, Visit 6A will be the start of the Extension Phase. Subjects who complete the Core Study, but who do not elect to immediately continue into the Extension Phase have up to 30 days after Visit 6A to participate. These subjects will be required to repeat selected assessments (Visit 6B) before being dispensed drug for the Extension Phase. Some subjects will have fewer visits based on the availability of lemborexant commercially. (revised per Amendment 05)

, ISWRD = Irregular Sleep-Wake Rhythm Disorder, V = Visit.

9.1.2 Prerandomization Phase

9.1.2.1 Optional Prescreening

There may be circumstances where the subject and/or caregiver is not sure whether the subject has an ISWRD pattern of sleep and wake, and would benefit from reviewing a report on the subject's sleep/wake pattern before agreeing to participate in the study. In these cases, the sites can offer the subject an opportunity to wear a designated activity tracker before consenting to the rest of the study procedures. A separate prescreening consent form would be signed by the subject and his/her legal representative for this purpose. After wearing the device for approximately 4 days, the subject and caregiver would be scheduled to return to the clinic so that the output from the device can be reviewed. At that time, the subject and caregiver would decide whether to participate in the study, which will require the study consent forms to be completed as described above. (revised per Amendment 05)

9.1.2.2 Screening Period

The maximum duration of the Screening Period will be 42 days. At the first visit, informed consent will be obtained after the study has been fully explained to each subject and caregiver and before the conduct of any screening procedures or assessments (see Optional Prescreening [above]). Subjects or their legal representative will sign the informed consent; caregivers must sign a separate consent form. The clinician will confirm that the subject meets diagnostic criteria for AD-D, based on the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines. If documentation of the AD diagnosis is not available, investigators may order a computed tomography (CT) scan and relevant blood tests to rule out other possible causes of dementia. A medical, psychiatric, and sleep history interview will be conducted, and will include confirmation that the subject meets diagnostic criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep Wake Type. Subjects will be administered the MMSE and the electronic version of the Columbia Suicide Severity Rating Scale (eC-SSRS), and will undergo the subject component of the Cornell Scale for Depression in Dementia (CSDD) interview. Additional eligibility criteria will be evaluated and clinical laboratory tests, ECG, vital signs, height, and weight will be assessed. Caregivers will be administered the caregiver input component of the CSDD. (revised per Amendments 03 and 05)

Eligible subjects will be provided with an actigraph (for actigraphy) to wear continuously throughout the study. They will be asked to provide a typical (habitual) time when the subject goes to sleep at night. (revised per Amendments 02 and 05)

The appropriate informants will be provided with a daily log (sleep period log) to note the start and end times of the subject's actual time in bed each day during the night and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. The informants will be trained in the use of the actigraph and the log. Site staff will instruct informants (1) in the evening, to fill in the times when the actigraph was not worn; and (2) in the morning, to fill out the bedtimes and morning rise times, and will emphasize the importance of doing so. Sites will also arrange for the subject to undergo a diagnostic sleep study either at a sleep center or at home to determine the presence or

absence of sleep apnea, unless one has been obtained within the previous 6 months. Before randomization, the investigator will be required to review a report detailing the subject's apnea-hypopnea index. (revised per Amendments 01, 02, 03, and 05)

After subjects have worn the actigraph for at least 14 days, caregivers will return to the clinic. The actigraph data will be downloaded and transmitted to the central reader along with the sleep log of bedtimes, morning wake times, and times when the actigraph was replaced on the subject's wrist. Adverse events and concomitant medication use will be recorded. The sites will keep the actigraph at the clinic until the Baseline visit, when the device will again be provided to the subjects. The central scoring will determine whether the data from the screening period meet the quality standards required by the inclusion criteria. (revised per Amendment 05)

During the Screening Period, subjects who meet the eligibility criteria for ISWRD on the basis of actigraphy and are not excluded on the basis of the diagnostic sleep study for sleep apnea will then be scheduled for the Baseline visit. Subjects who did not meet eligibility criteria based on actigraphy may be rescreened, following consultation with the Sponsor, as long as they were not excluded based on apnea-hypopnea index (AHI). (revised per Amendments 01 and 05)

9.1.2.3 Baseline Period

On Day 1, the Screening Period will end and the Baseline Period will take place. The Baseline visit must occur no earlier than 2 days and no later than 27 days after Visit 2 (caregiver visit), and may be scheduled across 2 consecutive days if necessary. Clinical laboratory tests, an ECG, vital signs, AEs, concomitant medications, and weight will be assessed. The site on the arm where the actigraph is applied will be examined. A plasma sample will be obtained from any subject taking any cognitive enhancer(s) and will be used to measure plasma concentrations of the enhancer(s). As proxy for the subject, caregivers will complete the SDI, NPI-10 and the EQ-5D-5L (Proxy Version 1). The caregiver will also complete the EQ-5D-5L, ZBI-short, and the PSQI for himself/herself. The subject will be administered the ADAS-cog and the EQ-5D-5L (Self version). The rater will complete the baseline assessment for the CGIC-ISWRD Scale. (revised per Amendment 01 and 03)

9.1.3 Randomization Phase

9.1.3.1 Treatment Period

The Treatment Period will begin on the evening of Day 1 and will continue for 4 weeks. Subjects will be randomized, in a double-blind manner, to receive LEM2.5, LEM5, LEM10, LEM15, or PBO. Study drug will be dispensed to the caregiver. During the Treatment Period, subjects will take study drug each night immediately (ie, within 5 minutes) before bedtime (defined as the median bedtime [median calculated bedtime (MCB)], calculated based on the sleep log during Screening). Time of dosing will be collected on the sleep log and entered by the sites into the appropriate electronic case report form (eCRF). (revised per Amendments 01 and 05)

After approximately 2 weeks of the Treatment Period, caregivers and subjects will return to the clinic. The actigraph data will be downloaded and transmitted to the central reader along with the sleep log. Vital signs will be assessed at this visit. Adverse events, treatment compliance, and concomitant medication use will be recorded. The site on the arm where the actigraph is applied will be examined.

If the subject experiences an AE that results in a temporary discontinuation of study medication, a rechallenge is possible following consultation with the Medical Monitor. (revised per Amendment 05)

At the end of 4 weeks, subjects will return to the clinic with their caregivers for end of Treatment Period assessments. The site on the arm where the actigraph is applied will be examined. Clinical laboratory tests, an ECG, vital signs, and weight will be assessed, and AEs and concomitant medications will be recorded. Treatment compliance will be assessed. As proxy for the subject, caregivers will complete the SDI, NPI-10 and the EQ-5D-5L (Proxy Version 1). The caregiver will also complete the EQ-5D-5L, ZBI-short, and PSQI for himself/ herself. Subjects will be administered the ADAS-cog, MMSE, EQ-5D-5L, and the eC-SSRS. A PK sample will be obtained. The CGIC-ISWRD Scale rater will complete the CGIC-ISWRD Scale. Actigraphy data will be downloaded, and the actigraph will be returned to the subject for the Follow-Up Period. (revised per Amendment 01)

During the End of Treatment visit, the study staff will discuss the Extension Phase with potentially eligible subjects and caregivers. (revised per Amendment 05)

9.1.3.2 Follow-Up Period

The Follow-Up Period will begin when subjects leave the clinic at the end of the Treatment Period. Subjects will cease taking study drug but will continue to wear the actigraph until the End of Study visit.

At least 14 days but no more than 18 days after the end of the Treatment Period, subjects and caregivers will return to the clinic for the End of Study Visit. Clinical laboratory tests, an ECG, vital signs, and weight will be assessed, AEs and concomitant medication use will be recorded, and the site on the arm where the actigraph is applied will be examined. Actigraphy data will be downloaded and transmitted to the central reader along with the sleep log.

A subject who prematurely discontinues taking study drug should return to the clinic as soon as possible after discontinuing study drug, to complete an Early Termination Visit and a Follow-Up Visit after 14 days. If the subject discontinues from the study due to an AE, the subject must complete an Early Termination Visit, and the AE must be followed to resolution or for 2 weeks, whichever comes sooner. (revised per Amendment 05)

9.1.4 Extension Phase

The Extension Phase will provide supportive data on the safety and tolerability of lemborexant in the long-term treatment of ISWRD in subjects with AD. The Extension Phase will consist of a 30-month Maintenance Period and a 14-day Follow-Up Period.

Subjects who complete the Core Study EOS Visit within 30 days prior to enrollment in the Extension Phase will be eligible for enrollment. (revised per Amendment 05)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Rationale for Efficacy Assessments

Irregular Sleep-Wake Rhythm Disorder (ISWRD) is clinically differentiated from insomnia (Section 7.1.1). Therefore, although Study E2006-G000-202 (Study 202) includes typical insomnia endpoints, these endpoints only relate to nighttime sleep and are not sufficient to assess ISWRD. In Study 202, both sleep efficiency and wake efficiency will be calculated. In addition to aSE and aWE, actigraphy also provides sleep fragmentation and activity indices, which can help determine the effect of treatment. While the primary efficacy analyses will be conducted on data from the end of treatment, actigraphy data will also be analyzed during each week to detect the onset of efficacy.

9.2.2 Rationale for Subject Population

Patients with AD-D constitute the subject population (Section 7). Irregular Sleep-Wake Rhythm Disorder occurs in other types of dementia besides AD-D. However, the Lewy Body Dementias, which include both Dementia with Lewy Bodies and Parkinson's Disease Dementia, are associated with REM behavior disorder, a sleep disorder in which the normal inhibition of the motor muscles during REM sleep is reduced, allowing bodily movement. As a result, patients can act out their dreams, putting them and their bed partners at risk of bodily injury. These subjects are, therefore, excluded from participation, as are subjects with Parkinson's disease (a Lewy body disorder) even without Parkinson's Disease Dementia, and any subject with a history of REM behavior disorder within the previous year, or with evidence of REM behavior disorder from the diagnostic recording.

9.2.3 Rationale for Dose Selection

The rationale for dose selection is explained in Section 9.4.4.

9.2.4 Rationale for Duration of Treatment

In the Core Study, subjects will be treated for 4 weeks. Based on data from Study 201, it would be expected that nocturnal sleep variables may improve early in treatment, since lemborexant was efficacious after the first 2 doses. However, it may take longer for the daytime variables to improve. (revised per Amendment 05)

In the Extension Phase, treatment will last for a maximum duration of 30 months, until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued. (revised per Amendment 05)

9.2.5 Rationale for Study Endpoints

As noted, ISWRD is not insomnia. While this study includes typical insomnia endpoints, these are not sufficient to assess ISWRD, since these endpoints only relate to nighttime sleep. In Study 202, both sleep efficiency and wake efficiency will be derived from actigraphy, since assessment requires recording throughout the 24-hour day. In addition to aSE and aWE, actigraphy also provides sleep fragmentation and activity indices, which can help determine the effect of treatment. During the nocturnal sleep period, sleep and wake bouts will be assessed to determine whether subjects are able to return to sleep more quickly at night.

9.2.6 Randomization

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

9.2.7 Study Controls

A placebo control has been incorporated into the study design in a 1:1:1:1:1 ratio. Subjects receiving placebo will undergo the same procedures as subjects receiving lemborexant. No active control is available as there are no currently approved treatments for ISWRD.

9.2.8 Adjudication Committee (revised per Amendment 02)

An independent Adjudication Committee will be employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure will be used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [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 Amendments 02 and 06)

9.3 Selection of Study Population

It is expected that approximately 230 subjects will be screened to provide approximately 60 randomized subjects at approximately 60 sites in the US, EU, and Japan. 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. (revised per Amendments 01, 04, 05, and 06)

9.3.1 Inclusion Criteria for Subjects (revised per Amendment 05)

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

1. Male or female, age 60 to 90 years at the time of informed consent (revised per Amendment 01)
2. Able to provide informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, if required in accordance with local laws, regulations and customs, and the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations).
3. Documentation of diagnosis with Alzheimer's disease dementia on the basis of the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines
4. MMSE 10 to 26 at Screening (revised per Amendments 01 and 03)
5. Meets criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (DSM-5) and the 10th revision of the ICD-10, as follows: Complaint by the subject or caregiver of difficulty sleeping during the night and/or excessive daytime sleepiness associated with multiple irregular sleep bouts during a 24-hour period (revised per Amendment 03)
6. Frequency of complaint of sleep and wake fragmentation ≥ 3 days per week
7. Duration of complaint of sleep and wake fragmentation ≥ 3 months
8. During the Screening Period, mean aSE <87.5% within the defined nocturnal sleep period and mean aWE <87.5% during the defined wake period (revised per Amendments 02 and 05)
9. Confirmation by actigraphy of a combination of sleep bouts of >10 minutes during the wake period plus wake bouts of >10 minutes during the sleep period, totaling at least 4 bouts per 24 hours period, ≥3 days per week
10. Ambulatory and living in the community or in a residence not classified as a skilled nursing facility (an assisted living facility with separate living quarters for subjects and caregiver or informants is acceptable) (revised per Amendment 01)
11. Willing not to start a behavioral or other treatment program for sleep or wake difficulties and not to start a new treatment for other symptoms of AD-D during participation in the study
12. Has a reliable and competent caregiver (or caregiver or informants) who can accompany the subject to study visits, administer study medication on a nightly basis and provide information on the status of the subject (revised per Amendment 01)
13. For subjects taking a cholinesterase inhibitor and/or memantine, dosing regimen must have been stable for at least 3 months

Inclusion Criteria for Caregivers (per Amendment 05)

Caregivers must meet all of the following inclusion criteria for subjects to be included in the study:

14. Able to provide informed consent
15. Spends at least 10 hours per week with the subject (revised per Amendment 01)
16. Able to meet caregiver requirements (Subject Inclusion Criterion #13)
17. Willing to provide information on himself/herself regarding sleep quality and caregiver burden

9.3.2 Exclusion Criteria for Subjects (revised per Amendment 05)

1. A diagnosis of vascular dementia, dementia following multiple strokes, or any synucleinopathy/Lewy body disorder. This includes Dementia with Lewy Bodies and Parkinson's disease with or without dementia.
2. A current diagnosis of moderate to severe obstructive sleep apnea (OSA) or central sleep apnea, or current use of continuous positive airways pressure even if mild severity of OSA, restless legs syndrome, or narcolepsy
3. An Apnea-Hypopnea Index or equivalent ≥15 events/hour on diagnostic sleep study conducted prior to Baseline or within 6 months of Screening
4. A clinically significant movement disorder that would affect the differentiation of sleep and wake by the actigraphy analytic algorithm
5. Current symptoms or history during the past year of Rapid Eye Movement (REM) Behavior Disorder or sleep-related violent behavior
6. Probable Major Depression, as evidenced by score >10 on the CSDD at Screening
7. Unable to tolerate wearing the actigraph. At a minimum, subjects must be able to wear the actigraph for 5 complete days out of 7 days' data. A day will be considered complete as long as data from 90% of the 24-hour period are able to be scored.
8. Excessive caffeine use that in the opinion of the investigator contributes to the subject's ISWRD
9. History of drug or alcohol dependency or abuse within approximately the previous 2 years
10. Reports habitually consuming more than 14 drinks containing alcohol per week or habitually consumes alcohol within 3 hours before bedtime and unwilling to limit alcohol intake to 2 or fewer drinks per day or to forego having alcohol within 3 hours before bedtime for the duration of his/her participation in the study
11. Known to be human immunodeficiency virus positive
12. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
13. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated ECG at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms) (subjects with

evidence of bundle branch block are not excluded if the block is not clinically significant, as documented by the investigator in the source document) (revised per Amendment 01)

14. Current evidence of clinically significant disease that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
15. Any history of a medical or psychiatric condition other than AD-D that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
16. History of malignancy within the previous 5 years except for adequately treated basal cell or squamous cell skin cancer or cervical carcinoma in situ
17. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering "Yes" to questions 4 and 5 on the Suicidal Ideation section of the eC-SSRS.
18. Any suicidal behavior in the past 10 years based on the eC-SSRS (revised per Amendment 01)
19. History of violence toward the caregiver or others
20. Scheduled for surgery using general anesthesia during the study (revised per Amendment 03)
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before starting actigraphy during Screening (A list of prohibited concomitant medications is presented in Appendix 3 of the protocol)
22. Used any modality of treatment for ISWRD between Screening and Randomization, based on approaches related to circadian rhythms, including phototherapy (light therapy), melatonin and melatonin agonists (revised per Amendment 03)
23. Failed treatment with Belsomra® (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones between Screening and Randomization, or plans to travel across more than 3 time zones during the study
25. Hypersensitivity to lemborexant or to its excipients
26. Currently enrolled in another clinical trial, except for observational studies with no treatment component (revised per Amendment 01)
27. Used any investigational drug or device before informed consent (ie, within 30 days or 5× the investigational drug half-life whichever is longer or 6 months for potential disease-modifying drugs)
28. Previously participated in any clinical trial of lemborexant

9.3.3 Removal of Subjects from Therapy or Assessment

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

A subject who discontinues study treatment should complete the set of end-of-treatment procedures, and protocol-specified information will be collected. 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 eCRF page. In addition, the date of last dose of study drug(s) will be recorded.

9.4 Treatments

9.4.1 Treatments Administered (revised per Amendment 05)

Core Study

Lemborexant 2.5 mg, 5 mg, 10 mg, 15 mg or lemborexant-matched placebo treatments will be taken orally in tablet form each night for 28 consecutive nights immediately (ie, 5 minutes) before the time the subject intends to try to sleep. All subjects will receive 2 tablets as described below, according to the treatment arm to which the subject has been randomized:

- LEM2.5: one lemborexant 2.5-mg tablet and one lemborexant-matched placebo tablet
- LEM5: one lemborexant 5-mg tablet and one lemborexant-matched placebo tablet
- LEM10: one lemborexant 10-mg tablet and one lemborexant-matched placebo tablet
- LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet
- PBO: two lemborexant-matched placebo tablets

9.4.2 Identity of Investigational Products

The sponsor will provide lemborexant tablets in strengths of 2.5 mg, 5 mg, 10 mg and lemborexant-matched placebo, identical in appearance. Tablets will be packaged in blister packs in a double-blind manner. For US and EU sites only, the blister packs will be child resistant. (revised per Amendment 04)

Each subject will be dispensed a single pack at on Day 1. The subject will take 2 tablets a day; in a combination of 2.5 mg, 5 mg and 10 mg lemborexant tablets or lemborexant-matched placebo tablets. Each pack will contain a 33-day supply of tablets in double-blind fashion.

Extension Phase

Details on treatments administered during the Extension Phase are provided in Appendix 4. (revised per Amendment 05)

9.4.2.1 Chemical Name, Structural Formula of E2006

- Test drug code: E2006

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

9.4.2.2 Comparator Drug

Placebo to match lemborexant

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 must 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 (or if regionally required, the head of the medical institution) 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

Approximately 60 subjects will be randomized to one of the following treatment arms: PBO, LEM2.5, LEM5, LEM10, or LEM15, in an approximate 1:1:1:1:1 ratio, stratified by country. Randomization will be based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.4.4 Selection of Doses in the Study

The primary objective is to characterize the dose response of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO. The doses were chosen based on those included in the insomnia Phase 3 program (LEM2.5, LEM5 and LEM10). A higher dose (LEM15) was also included because this is a new population for studies of lemborexant. If LEM15 is associated with unexpected tolerability issues, sufficient preliminary data from lower doses of lemborexant will be available upon which to assess efficacy and inform dose selection for the Phase 3 program.

9.4.5 Selection and Timing of Dose for Each Subject

Lemborexant 2.5 mg, 5 mg, 10 mg, 15 mg or lemborexant-matched PBO treatments will be taken orally in tablet form each night for 28 consecutive nights immediately before the time the subject intends to try to sleep. All subjects will receive 2 tablets.

9.4.6 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure.

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

9.4.7 Prior and Concomitant Therapy

Potential subjects who are taking a cholinesterase inhibitor and/or memantine will be allowed in the study provided that the treatment regimen has been stable for at least 3 months.

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.

9.4.7.1 Drug-Drug Interactions

Not applicable

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Prohibited medications include anticholinergic drugs, moderate and strong CYP3A inhibitors and all CYP3A inducers. Prohibited therapies include any treatment for ISWRD based on modifying circadian rhythms, including bright light therapy, melatonin and melatonin agonists. In this context, phototherapy refers specifically to the use of timed bright light as a therapeutic intervention. (revised per Amendments 03 and 06)

Medications that are used to treat behaviors associated with ISWRD, such as antipsychotic medications or trazodone, are permitted provided that the subject has been taking a stable dose for at least 1 month. The prohibition applies even if the entire class to which that medication belongs is not prohibited (eg, anticonvulsants). (revised per Amendment 03)

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

If a subject starts any prohibited medication or therapy that would compromise the safety of the subject, he/she must discontinue from the study, with the exception that certain prohibited medications may be used for a short duration (not to exceed 2 weeks) to treat an acute condition if this is agreed with the Medical Monitor. Note that moderate and strong CYP3A inhibitors and CYP3A4 inducers will not be permitted at any time for any duration during the study. (revised per Amendment 06)

Rescue medications will be permitted to treat significant agitation or anxiety. They should be used for the shortest period of time, and no more than 3 days per week, and at the lowest possible dose. If not used daily, benzodiazepines and non-benzodiazepine hypnotics and antipsychotics may be used as rescue medications. Before prescribing, whenever practicable, the investigator should discuss the proposed rescue medication with the Medical Monitor. The timing of the study visit following the use of rescue medication should be adjusted if a rescue medication has been taken within 24 hours of the scheduled visit. (revised per Amendment 03)

9.4.8 Treatment Compliance

Compliance will be assessed by examination of blister packs returned to the investigator at the end of the Treatment Periods.

All caregivers 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.

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) 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 (or if regionally required, the head of the medical institution or the designated pharmacist) 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, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vita of the Principal Investigator (PI), including a copy of the PI's current medical license or medical registration number on the curriculum vita
- A signed and dated clinical studies agreement

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

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

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA; Medicine and Healthcare products Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

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

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

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

9.5.1.2 Screening Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

A medical, psychiatric, and sleep history interview will be conducted at the Screening Visit, and will include confirmation that the subject meets diagnostic criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep Wake Type. All sleep, medical, and psychiatric history must be noted in the Medical History and Current Medical Conditions eCRF.

Physical examinations (full or brief) will be performed as described in Section 9.5.1.5.

9.5.1.2.2 CORNELL SCALE FOR DEPRESSION IN DEMENTIA

The subject component of the CSDD interview will also be administered at Screening. Caregivers will be administered the caregiver input component of the CSDD. The CSDD (Alexopoulos et al., 1988) derives information from the patient and the informant (caregiver) to assess signs and symptoms of major depression in patients with dementia. Information is elicited through two semi-structured interviews; an interview with an informant and an interview with the patient, both of which focus on depressive symptoms and signs that occurred during the week preceding the interview. The final ratings of the CSDD items represent the rater's clinical impression rather that the responses of the informant or the patient. The CSDD, which takes approximately 20 minutes to administer, assesses a total of 19 items in the following 5 categories: mood-related signs, behavioral disturbance, physical signs, cyclic functions, and ideational disturbance. Each item within each category is rated for severity on a scale of 0-2 (0=absent, 1=mild or intermittent, 2=severe). The item scores are added. Scores above 10 indicate a probable major depression. Scores above 18 indicate a definite major depression. Scores below 6 are associated with absence of significant depressive symptoms.

9.5.1.2.3 VIRAL TEST

Viral testing for hepatitis B and C will be conducted from a 6-mL 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, with confirmation as needed using the HCV score. (revised per Amendment 05)

9.5.1.3 Efficacy Assessments

9.5.1.3.1 ACTIGRAPHY (REVISED PER AMENDMENT 05)

An actigraph is a device that consists of a compact, wrist-worn, battery-operated activity monitor which looks like a wrist watch. This device incorporates a multidirectional accelerometer to monitor degree and intensity of motion. Data from an actigraph can be fitted to an algorithm from which rest / activity patterns can be derived.

Eligible subjects will be provided with an actigraph (for actigraphy) to wear continuously throughout the study. Informants will be provided with a daily log (sleep period log) for noting the start and end times of nocturnal sleep periods and to log the approximate times that the actigraph was replaced on the subject's wrist, if inadvertently removed. Informants will be trained in the use of the actigraph and the log. Site staff will instruct informants (1) in the evening, to fill in the times when the actigraph was not worn; and (2) in the morning, to fill out the bedtimes and morning rise times, and will emphasize the importance of doing so. (revised per Amendments 01, 02, 03, and 05)

A central actigraphy reader will score daily actigraphy records using a customized algorithm. The in-bed intervals will be provided to the central reader based on the sleep logs completed by the caregivers. The actigraphy data obtained during the Screening Period will be used to a) determine eligibility and b) derive baseline actigraphy parameters for those subjects who are randomized. The nocturnal sleep period will be defined for each subject as the 8 hours starting at the subject's MCB, calculated from the sleep log completed during screening. (revised per Amendment 05)

Also note that the calculated MCB will determine time of dosing for a given subject such that the dose each night should be taken within 5 minutes before bedtime. (revised per Amendments 01 and 05)

Actigraphy parameters are as follows:

- Sleep efficiency (aSE): 100% × the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours (revised per Amendment 05)
- Sleep fragmentation index (SFI) from actigraphy: The SFI will be calculated as the sum of a Movement Index (MI) and a Fragmentation Index (FI), with MI = (epochs of wake per TIB)*100 and FI = (number of ≤1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period)*100. (revised per Amendments 01 and 05)
- Wake fragmentation index (WFI) from actigraphy: The WFI will be calculated as the sum of an Immobility Index (II) and a FI, with II = (epochs of immobility per the 16 hours outside of the defined sleep period)*100 and FI = (number of ≤1-minute periods of mobility/total number of periods of mobility the 16 hours outside of the defined sleep period)*100. (revised per Amendments 01 and 05)
- Wake efficiency (aWE): 100% × the total duration of wake epochs during the defined wake period (ie, the 16 hours outside of the predefined sleep period) divided by 16 hours (revised per Amendment 05)
- Mean Duration of Wake Bouts (aMeanDurWB): average duration of all wake bouts (with wake bout defined as continuous wake of 10 minutes or longer) that occur during the defined nocturnal predefined sleep period (revised per Amendment 05)
- Mean Duration of Sleep Bouts (aMeanDurSB): average duration of all sleep bouts (with sleep bout defined as continuous sleep of 10 minutes or longer) that occur during the 16 hours outside of the predefined nocturnal sleep period (revised per Amendments 01 and 05 and Administrative Change)
- Intradaily Variability (IV): gives an indication of ISWRD by quantifying the number and strength of transitions between rest and activity bouts, with a higher number indicating more fragmentation; derived by the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance)

- Interdaily Stability (IS): gives an indication of the stability of the sleep-wake rhythm across days, and varies from zero (low stability) to 1 (high stability); derived by the ratio between the variance of the average 24-hour pattern around the mean and the overall variance
- L5: the average activity across the least active 5-hour period per 24 hour period, with high values indicating restlessness
- M10: the average activity during the most active 10-hour period per 24 hour period with low levels indicating inactivity
- AMP: amplitude of the rest-activity rhythm calculated as the difference between M10 and L5
- RA: relative amplitude of the rest-activity rhythm calculated as the difference between M10 and L5 divided by M10 plus L5

9.5.1.3.2 CLINICIAN'S GLOBAL IMPRESSION OF CHANGE IRREGULAR SLEEP-WAKE RHYTHM DISORDER (CGIC-ISWRD) SCALE (REVISED PER AMENDMENT 01)

The CGIC-ISWRD Scale uses the standardized methodology for obtaining global clinical ratings, and is an assessment conducted by an independent rater at the end of the treatment period who has no access to the source data or other psychometric test scores conducted as part of the given protocol. The instrument consists of 3 parts: a guided baseline interview administered to the subject and an informant, a follow-up interview administered to the subject and an informant, and a clinician's rating review. The informant must be a person who knows the subject well. The baseline interview serves as a reference for future ratings. During the baseline interview, the rater will evaluate subjects regarding domains of (1) sleep and wake symptoms; (2) mood and behavioral symptoms; (3) attention/arousal; and (4) social functioning. In the follow-up interview, a 7-point scale is used, from 1 = marked improvement, 4 = no change, to 7 = marked worsening, to score each of the four domains and to provide an overall score. The overall score is used to address the secondary objective; the domain scores are exploratory. In this study, the assessment will focus on the symptoms of ISWRD, not the general condition of dementia.

9.5.1.3.3 NEUROPSYCHIATRIC INVENTORY (NPI-10) (REVISED TO BE AN EFFICACY ASSESSMENT PER AMENDMENT 05)

The NPI-10 (Trzepacz et al., 2013) assesses a wide range of behaviors seen in dementia for both frequency and severity. These include delusions, agitation, depression, irritability and apathy. The scale takes 10 minutes for a clinician to administer. This scale will be administered with the caregiver as proxy for the subject. The NPI-10 has good psychometric properties and is widely used in drug trials. (revised per Amendment 01)

9.5.1.3.4 MINI MENTAL STATE EXAMINATION (REVISED TO BE AN EFFICACY ASSESSMENT PER AMENDMENT 05)

The MMSE (Folstein et al., 1975) is a cognitive instrument commonly used for screening purposes. It is a 30-point scale with higher scores indicating less impairment and lower

scores indicating more impairment. Seven items are assessed that measure orientation to time and place, registration, recall, attention, language and drawing. The MMSE will be administered to the subject by site staff.

9.5.1.3.5 ALZHEIMER'S DISEASE ASSESSMENT SCALE-COGNITIVE (ADAS-COG) (REVISED TO BE AN EFFICACY ASSESSMENT PER AMENDMENT 05)

The ADAS-cog (Rosen et al., 1984) is the most widely used cognitive scale in Alzheimer's disease trials. It is a structured scale that evaluates memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, ability to remember test instructions, maze, and number cancellation are also obtained. The modified version (ADAS-cog-13) used in this study is scored from 0 to 90 points with a score of 0 indicating no impairment, and a score of 90 indicating maximum impairment.

9.5.1.3.6 SLEEP DISORDERS INVENTORY (SDI) (REVISED TO BE AN EFFICACY ASSESSMENT PER AMENDMENT 05)

The SDI (Tractenberg et al, 2003) is an expanded version of one item of the NPI. It describes the frequency, severity, and caregiver burden of sleep-disturbed behaviors during a period prior to its administration. The SDI consists of the seven subquestions from the NPI sleep disturbance item. Each of the subquestions is a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-participant for the 2 weeks prior to the visit.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

A blood sample (4 mL) for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 will be taken at the end of treatment visit (Visit 5). The time and date of the 2 most recent doses before this sample and the time and date of the sample will be documented.

One blood sample (approximately 4 mL) will be obtained at Baseline (Visit 3) for only those subjects taking specific cognitive enhancers (ie, donepezil or galantamine or memantine alone or both donepezil and memantine or both galantamine and memantine). Another blood sample (approximately 4 mL) will be obtained at Visit 5 or ET for all subjects to measure lemborexant and its metabolites, as well as cognitive enhancers, as appropriate. (revised per Amendments 03 and 05)

For those subjects taking donepezil, the date and time of the 2 most recent doses of donepezil will be documented. For all subjects taking lemborexant, the date and time of the 2 most recent doses of lemborexant will also be documented.

In case of early termination due to safety or any other reasons, a plasma sample for lemborexant (and its metabolites), and for any cognitive enhancer (as applicable) will be taken from the subject.

PK sample collection, processing and handling will be detailed in a laboratory manual to be provided to the study sites or be incorporated in the central labs manual.

9.5.1.4.2 PHARMACODYNAMIC ASSESSMENTS

For modeling purposes, the change from baseline at the last week of treatment for the following efficacy variables aSE, aWE, SFI, WFI, IV, IS, AMP and RA will be treated as PD variables.

9.5.1.4.3 PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

For PK/PD assessments, the following efficacy variables aSE, aWE, SFI, WFI, IV, IS, AMP and RA will be treated as PD variables.

9.5.1.4.4 PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Blood samples for genotyping and for additional exploratory analyses will be obtained at Baseline from consenting subjects. Further details are provided in Appendix 2.

9.5.1.5 Safety Assessments

All subjects will undergo routine safety assessments at specified visits, including monitoring, questioning and recording of AEs, 12-lead ECGs, vital signs, weight, clinical hematology and chemistry analyses and urinalysis, and suicidality, assessed using the eC-SSRS.

9.5.1.5.1 ADVERSE EVENTS

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

The criteria for identifying AEs in this study are:

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

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

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

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

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such. (revised per Amendment 02)

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

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

All AEs must be followed for 14 days after the subject's last dose, or until resolution, whichever comes first.

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

ASSESSING SEVERITY OF ADVERSE EVENTS

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

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

The criteria for assessing severity are different than those used for seriousness (see below, this Section, 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

9.5.1.5.2 CLASSIFICATION OF CAUSALITY

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

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

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

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

9.5.1.5.3 SERIOUS ADVERSE EVENTS

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

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

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

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

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

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

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

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

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests are to be performed according to the schedule in Table 3.

Blood and urine samples will be collected for the clinical laboratory tests as listed in Table 1.

Subjects should be in a seated or supine position during blood collection. Blood volumes are listed in Table 2.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium

Table 1 Clinical Laboratory Tests

Category	Parameters
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, globulin, glucose, iron, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

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

Table 2 Blood Sampling Volumes for Laboratory and Pharmacokinetic Assessments (revised per Amendments 03 and 05)

	Approximate Volume per Sample (mL)	Collection Timepoints	Total Volume Collected (mL)
Clinical laboratory tests	12	Screening Baseline Visit 5 End of Study or ET	48
Viral tests	6	Screening	6
Pharmacogenomic testing	6	Baseline	6
Pharmacokinetic sampling	4	Baseline Visit 5 or ET visit	8
		Total	68
Extension Phase			
Clinical laboratory tests	12	Visit 6A or 6B, Visits 9, 12, 15, 18, 19, 20, 21, 22, 23, 24, and 25 (End of Study for the Extension Phase)	144

ET = early termination

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5) and the case report form (CRF) Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

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

9.5.1.5.5 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]) and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 3) by a validated method. Blood pressure and pulse will be measured after the subject has been 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) will be measured only at Screening.

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

9.5.1.5.6 PHYSICAL EXAMINATIONS

At Screening and at the end-of-study visit, a full physical examination will be conducted, including evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin. The full physical examination will include a brief neurological examination to assess possible impairment in major functions (ie, motor, cerebellar, sensory, major pathological reflexes). A urogenital examination will only be required in the presence of clinical symptoms related to this region and at the discretion of the investigator. At other study visits as designated in Table 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 Adverse Event eCRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/ Assessments (Table 3) and before blood samples are collected.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Event eCRF.

For ECG abnormalities meeting criteria of an SAE, 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]).

9.5.1.5.8 OTHER SAFETY ASSESSMENTS (REVISED PER AMENDMENT 05)

ELECTRONIC COLUMBIA-SUICIDE SEVERITY RATING SCALE (EC-SSRS)

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

MORNING RESIDUAL EFFECTS

To assess morning residual effects, activity levels from the 1st 3 hours after waketime from the first 3 days of the first week of treatment and the last 3 days of treatment will be compared with the mean activity levels from the 1st 3 hours after waketime during the actigraphy baseline period.

9.5.1.6 Other Assessments

9.5.1.6.1 EQ-5D-5L

The EQ-5D-5L 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 EuroQol Group, 1990; Brooks, 1996). The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

Three forms will be collected per subject per visit:

- Subject Self Version
  - The form will not be labeled Self Version but the wording will be for self-completion.
  - Caregivers or study coordinators can provide assisted self-completion services to the subject where the subject has physical impairments (eg, arthritis, severe visual impairment) that prevent self-completion. Assistance can be in the form of reading the instructions, questions, and responses verbatim (without interpretation) and in the order provided on the questionnaire. Assistance can be in the form of recording responses of the subject.
  - To be considered self-completed, all responses must have come from the subject.

- Caregiver Self Version
  - The caregiver completes the standard version regarding his/her own health status.
  - Study coordinators may provide assisted self-completion services as described above for physically impaired caregivers.
- Caregiver Proxy 1 Version
  - During the Core Study only, the caregiver completes the both the Self Version (regarding the caregiver) and the Proxy version (regarding the caregiver's perception of the subject's health status).
  - Study coordinators may provide assisted self-completion services as described above for physically impaired caregivers.

9.5.1.6.2 ZARIT BURDEN INTERVIEW – SHORT FORM

The ZBI – short version was developed from the full ZBI, to be suitable for caregivers of cognitively impaired older adults across diagnostic groups (Bédard et al., 2001). The ZBI can be used for cross-sectional, longitudinal, and intervention studies. It has been designed to reflect the stresses experienced by caregivers of dementia patients. It can be completed by caregivers directly or as part of an interview of the caregiver by the study coordinator. Caregivers are asked to respond to a series of 12 questions in 2 domains: personal strain and role strain. Each question is scored on a 5-point Likert scale from 0 to 4 (never to almost always). The range of summed scores is from 0 to 48. Higher scores reflect a higher feeling of burden.

9.5.1.6.3 PITTSBURGH SLEEP QUALITY INDEX

The PSQI (Buysse et al., 1989) is an instrument used to measure the quality and patterns of sleep in adults by measuring seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction, over the previous month. In scoring the PSQI, seven component scores are derived, each scored from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (range 0 to 21). Higher scores indicate worse sleep quality

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

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

Table 3 Schedule of Procedures/Assessments in Study E2006-G000-202 (revised per Amendments 01, 02, 05, and 06) (Core Study)

Phase	Prerandomization				Randomization					
Period	Optional Prescreen-ing	Screening		Baseline[a]	Treatment		Follow-Up		ET[f]	UN[g]
Visit	–1	1	2[b]	3	4	5[c]		6A[d,e]		
Study Day		-42 to -16	-27 to -2	1	10 to 18	29	30 to 42	43		
Procedures/Assessments										
Informed consent	X	X								
Activity tracker	X									
Inclusion/exclusion criteria	---------->									
Mini Mental State Exam[h]		X				X				
Cornell Scale for Depression in Dementia[i]		X								
Demographics		X								
Physical exam[j]		X		X		X		X	X	
Sleep, medical, and psychiatric history		X								
Prior / concomitant medications	---------->									
Height		X								
Weight		X		X	X	X		X	X	
Vital signs		X		X	X	X		X	X	
12-lead ECG		X		X		X		X	X	
Clinical laboratory tests and urinalysis		X		X		X		X	X	
Viral screening		X								

Table 3 Schedule of Procedures/Assessments in Study E2006-G000-202 (revised per Amendments 01, 02, 05, and 06) (Core Study)

Phase	Prerandomization				Randomization					
Period	Optional Prescreening	Screening		Baseline[a]	Treatment		Follow-Up		ET[f]	UN[g]
Visit	–1	1	2[b]	3	4	5[c]		6A[d,e]		
Study Day		-42 to -16	-27 to -2	1	10 to 18	29	30 to 42	43		
Procedures/Assessments										
eC-SSRS		X				X			X	X
Sleep Log	---------->									
Actigraphy	---------->									
Download actigraphy data			X		X	X		X	X	
ADAS-cog				X		X				
NPI-10[k]				X		X			X	
SDI[l]				X		X		**X**		
Diagnostic sleep study[m]		X								
EQ-5D-5L[n]				X		X				
PSQI[o]				X		X				
ZBI-short[o]				X		X				
CGIC-ISWRD Scale				X		X				
PK blood sampling[p]				X		X			X	
Randomization				X						
PG blood sample				X						
Dispense study drug				X				**X**		
Study drug at bedtime[q]				---------->						

Table 3 Schedule of Procedures/Assessments in Study E2006-G000-202 (revised per Amendments 01, 02, 05, and 06) (Core Study)

Phase	Prerandomization				Randomization					
Period	Optional Prescreening	Screening		Baseline[a]	Treatment		Follow-Up		ET[f]	UN[g]
Visit	–1	1	2[b]	3	4	5[c]		6A[d,e]		
Study Day		-42 to -16	-27 to -2	1	10 to 18	29	30 to 42	43		
Procedures/Assessments										
Study drug compliance					X	X				
Retrieve unused study drug						X				
Discharge from study								X	X	
Adverse events[r]	---------->									

ADAS-cog = Alzheimer's Disease Assessment Scale – Cognitive Subscale, CGIC-ISWRD = Clinician's Global Impression of Change-Irregular Sleep-Wake Disorder, CSDD = Cornell Scale for Depression in Dementia; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale,, EOS = End of Study, EQ-5D-5L = EuroQOL 5 Dimensions 5 Levels; ET = early termination, NPI-10 = Neuropsychiatric Inventory; PG = pharmacogenomics, PGI- C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PSQI = Pittsburgh Sleep Quality Index, PK = pharmacokinetic, SDI = Sleep Disorders Inventory, UN = unscheduled visit, ZBI = Zarit Burden Inventory

Footnotes for Table 3:

a: Baseline procedures can be scheduled across 2 days, with Day 1 being the first day of dosing. (revised per Amendment 01)
b: To be done at the end of 2 weeks of actigraphy and less than 2 days before the Baseline Visit
c: To be done within +4 days of the schedule
d: Assessments at Visit 6A are the baseline assessments for subjects entering the Extension Phase. Subjects may enter the Extension Phase up to 30 days after Visit 6A; however, those who do so must repeat these assessments at the time of enrollment (at Visit 6B [see Schedule of Assessments and Procedures for the Extension Phase]). (revised per Amendment 05)
e: Extension Phase study drug will be dispensed to subjects at Visit 6A who enter the Extension Phase directly after completing the Core Study. (revised per Amendment 05)
f: Subjects who discontinue the study early for any reason after Randomization should complete this visit.
g: Additional assessments may be conducted at this visit if the investigator considers them to be necessary.
h: The MMSE test instrument will be administered to subjects after informed consent has been obtained from caregivers and subjects and after caregiver eligibility has been established, but before clinical laboratory tests are drawn, so as to avoid performing venipuncture on subjects whose MMSE scores disqualify them from entry into the study. Informants are not required to provide informed consent. (revised per Amendment 01)
i: CSDD will be completed by interview with subject and with caregiver.
j: Full physical examination (including a brief neurological exam) will be conducted at Screening. An abbreviated physical examination will be conducted at other visits.
k: NPI-10 will be completed by the caregiver as proxy for the subject.
l: SDI will be completed by the caregiver as proxy for the subject. The SDI at Visit 6A will only be completed for subjects entering the Extension Phase. (revised per Amendment 05)
m: Diagnostic sleep study to be completed during Screening and reviewed by the investigator for the apnea-hypopnea index or equivalent, unless a diagnostic sleep study has been obtained within 6 months of the Screening visit (revised per Amendment 05)
n: EQ-5D-5L administered to the caregiver twice at each specified visit (once as proxy for the subject and separately for self) and once to the subject
o: PSQI and ZBI-short will be administered to the caregiver for self-completion.
p: One blood sample (approximately 4 mL) will be obtained at Baseline (Visit 3) for only those subjects taking specific cognitive enhancers (donepezil or galantamine or memantine alone or both donepezil and memantine or both galantamine and memantine). Another blood sample (approximately 4 mL) will be obtained at Visit 5 or ET for all subjects to measure lemborexant and its metabolites, as well as cognitive enhancers, as appropriate. (revised per Amendment 03).
q: Caregivers or Informants will administer study drug to subjects. All study drug administration must be within 5 minutes of bedtime (defined as the median calculated bedtime [MCB]). (revised per Amendments 01 and 06)
r: 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 9.2.8 Adjudication Committee. (revised per Amendment 02)

9.5.2.2 Description of Procedures/Assessments Schedule

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

9.5.3 Appropriateness of Measurements

The safety assessments to be performed in this study, including clinical laboratory tests, physical examinations, vital signs, ECG, and assessment of AEs are standard evaluations to ensure subject safety. The eC-SSRS is a standard assessment of suicidality in studies of CNS-active drugs. The CSDD is specifically designed to determine depressive symptomatology in patients with dementia. The NPI-10 and MMSE are also very common scales in dementia research to determine behavioral and cognitive symptoms.

Actigraphy is a standard measure used to record rest/activity patterns across multiple 24-hour periods, and has been used in basic research and clinical trials to evaluate the effectiveness of treatments.

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

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event. (revised per Amendment 05)

Serious adverse events, regardless of causality assessment, must be collected through the last visit in the Treatment Phase 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. (revised per Amendment 05)

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 to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

The female subject population will be exclusively postmenopausal.

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

9.5.4.3.2 Reporting of Study-Specific Events

There are no study-specific events.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

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

9.5.4.6 Regulatory Reporting of Adverse Events

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

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions will be reported, as required, to the competent authorities of all involved European member states. (revised per Amendment 04)

9.5.5 Completion/Discontinuation of Subjects

For analysis purposes, a subject will be considered to have completed the study once the assessments after the last dose of study drug have been completed.

The investigator or subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 3). In the event of discontinuation, the investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

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

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

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of one or both study drugs. Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5. 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 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, standard operating procedures, working practice documents, and applicable regulations and guidelines.

9.6.1 Data Collection

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

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

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

9.7.1 Statistical and Analytical Plans

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

The statistical analyses are described in this section. Further details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP). There will be 2 separate SAPs: 1 for the Core Study, and 1 for the Extension Phase. (revised per Amendment 05)

All statistical tests will be based on the 5% level of significance (2-sided), unless otherwise stated. If statistical comparisons are not defined, all pairwise comparisons will be tested.

9.7.1.1 Study Endpoints

9.7.1.1.1 SLEEP-RELATED ENDPOINTS (REVISED PER AMENDMENTS 05 AND 06)

The sleep-related endpoints are:

- The change from baseline of mean aSE with LEM compared to PBO during the last week of treatment. (revised per Amendments 01 and 06)
- The change from baseline of aSE during each week of treatment with LEM compared to PBO. (revised per Amendment 06)
- Change from baseline in mean SFI during each week of treatment. (revised per Amendments 01 and 06)
- Change from baseline of the aMeanDurWB during each week of treatment. (revised per Amendment 06)

9.7.1.1.2 WAKE-RELATED ENDPOINTS (REVISED PER AMENDMENTS 05 AND 06)

- The change from baseline of mean aWE with LEM compared to PBO during each week of treatment. (revised per Amendments 01 and 06)
- Change from baseline of the aMeanDurSB during each week of treatment. (revised per Amendment 06)
- Change from baseline of mean WFI during each week of treatment (revised per Amendments 01 and 06)

9.7.1.1.3 CIRCADIAN RHYTHM-RELATED ENDPOINTS (REVISED PER AMENDMENTS 05 AND 06)

- Change from baseline of IV, IS, L5, M10, AMP and RA over each week of treatment (revised per Amendments 01 and 06)

9.7.1.1.4 ADDITIONAL ENDPOINTS (REVISED PER AMENDMENT 06)

The following additional endpoints will be explored for LEM2.5, LEM5, LEM10 and LEM15 compared to PBO:

- Safety and tolerability of LEM, including AEs and SAEs
- Change from baseline in Clinician's Global Impression of Change-ISWRD (CGIC-ISWRD) Scale on symptoms of ISWRD total score and domains. (revised per Amendments 01 and 06)
- Change from baseline of the sum of activity counts and change from baseline in the number of bouts >10 minutes of sleep in the first 3 hours after morning waketime on the first 3 days and last 3 days of treatment
- Number and percentage of subjects in each category of the CGIC-ISWRD Scale at Day 29 (revised per Amendment 01)
- Rebound sleep and wake fragmentation endpoints as assessed from actigraphy during the Follow-Up Period
    - Change from baseline in mean aSE of the first 7 nights, and aSE of the second 7 nights of the Follow-Up Period
    - Change from baseline in mean aWE of the first 7 days and mean aWE of the second 7 days of the Follow-Up Period
    - Proportion of subjects whose mean aSE is higher than at baseline for the first 7 nights or the second 7 nights of the Follow-Up Period
    - Proportion of subjects whose mean aWE is longer than at baseline for the first 7 days or the second 7 days of the Follow-Up Period (revised per Amendment 03)
- Change from baseline on ADAS-Cog at Day 29
- Change from baseline on MMSE at Day 29
- Change from baseline sleep quality in caregivers as measured by the PSQI at Day 29
- Change from baseline of caregiver burden on all scores of the ZBI-short form at Day 29. (revised per Amendment 06)
- Change from baseline on the EQ-5D-5L utility and Visual Analogue Scale (VAS) scores at Day 29 for both subject and caregiver
- Change from baseline of the total score of NPI-10 at Day 29
- Change from baseline on SDI at Day 29
- Characterize the PK of lemborexant using the population approach and descriptive statistics for the plasma concentrations of its metabolites M4, M9, and M10. (revised per Amendment 06)

- Relationships between exposure to lemborexant, efficacy, and/or safety variables using PK/PD modeling
- Assess the plasma concentrations of cognitive enhancers and lemborexant in subjects taking both drugs.
- Evaluate the long-term safety and tolerability of flexible doses of LEM5, LEM10, and LEM15 per day over a period of 30 months in subjects with ISWRD who have completed the Core Study. (revised per Amendments 05 and 06)

9.7.1.2 Definitions of Analysis Sets

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

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

The PK Analysis Set is the group of subjects who have at least 1 quantifiable plasma concentration of lemborexant, with adequately documented dosing history.

The PK/PD Analysis Set is the group of subjects receiving either lemborexant or placebo who have efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant should have at least 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. Other reasons for study drug and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment group.

9.7.1.4 Demographic and other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, height, and weight; body mass index (BMI); categorical variables include sex, age group (<65, 65 to 74 years, 75 to 84 years, and 85 and older), BMI group, race, and ethnicity. Other baseline characteristics for actigraphy data and MMSE will also be summarized. (revised per Amendment 01)

If the Safety Analysis Set and FAS differ substantially, the demographic summaries will be repeated on the FAS.

9.7.1.5 Prior and Concomitant Therapy

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

Prior medications are defined as medications that stopped before the first dose of study drug, where study drug includes PBO.

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

9.7.1.6 Efficacy Analyses

9.7.1.6.1 ANALYSIS FOR THE SLEEP-RELATED, WAKE-RELATED, AND CIRCADIAN RHYTHM-RELATED ENDPOINTS (REVISED PER AMENDMENT 06)

The changes from baseline of the mean aSE for the last week of treatment and for each week of treatment, and the change from baseline for the mean aWE for the last week on treatment will be analyzed using MCP-MOD (Multiple Comparisons and Modelling) approach. Dose response models that will be evaluated are linear, linear log, quadratic, exponential, e_{max}, sigmoid e_{max}, beta and logistic. (revised per Amendments 05 and 06)

Analysis stage – MCP-step: Establish a dose-response signal (the dose-response curve is not flat) using multiple comparison procedure. Based on the observed data, the model that shows a statistically significant trend test will be selected (at one-sided 5% significance). If more than one is statistically significant, then the most optimal model using Akaike Information Criteria will be selected. This method prospectively controls the type I error at 5%.

Analysis Stage – Mod-step: Dose response and target dose estimation will be based on dose response modelling. MCP-MOD approach allows for interpolation between doses.

As a sensitivity analysis to the aSE and aWE endpoints mean aSE and mean aWE for Week 4 will be analyzed using the longitudinal data analysis (LDA). (revised per Amendment 06)

The change from baseline of the following endpoints will be analyzed using LDA on the FAS for LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, as appropriate: mean SFI, mean WFI, mean aSE, mean aWE, mean aMeanDurSB, mean aMeanDurWB, IV, IS, L5, M10, AMP, and RA. (revised per Amendment 06)

The model will include all data and will be adjusted for the corresponding baseline value, country, treatment, time (Week 1, Week 2, Week 3 and Week 4) and the interaction of treatment

by time. Treatment by time interaction will be used to construct the treatment comparisons at a specific time. The LDA model accounts for any missing data, and assumes that the missing data are missing at random. An unstructured covariance matrix will be used, and if the model fails to converge, then an autoregressive matrix will be used. Where data are normally distributed, least square (LS) means, difference in LS means of each lemborexant dose compared to PBO, 95% CIs and P values at the appropriate time point will be presented. (revised per Amendment 01)

Additional analyses, as deemed necessary, may include the investigation of subgroup analyses and/or addition of covariates to the model of age, sex, race, BMI, severity of aSE, severity of aWE, wake fragmentation, severity of AD-D based on MMSE and/or other subgroups. (revised per Amendment 06)

9.7.1.6.2 ANALYSES FOR ADDITIONAL ENDPOINTS (REVISED PER AMENDMENT 06)

The overall score of CGIC-ISWRD Scale at Day 29 will be analyzed using the Cochran–Mantel–Haenszel test, adjusted for country. (revised per Amendment 01)

To assess residual morning sleepiness levels, change from baseline in the sum of activity counts in the 3 hour interval after morning waketime will be compared for each treatment group relative to placebo for each of the 6 mornings comprising the first 3 days and last 3 days of treatment. The change from baseline will be analyzed using analysis of covariance (ANCOVA), with treatment and baseline as fixed effects. LS means, difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% CIs, and p-values will be presented. (revised per Amendment 06) In addition, the change from baseline will be analyzed using ANCOVA for the number of bouts >10 min scored as sleep will be determined counts in the 3 hour interval after morning waketime, for each of the 6 mornings comprising the first 3 days and last 3 days of treatment. (revised per Amendment 06)

Rebound sleep and wake fragmentation are defined as worsened aSE or aWE compared to baseline after study drug treatment is completed. Actigraphy data from the Follow-Up Period will be compared to actigraphy data from the baseline to assess whether subjects experience rebound sleep or wake fragmentation. Specifically, a lower value for aSE or aWE during the Follow-Up Period compared to the mean aSE or aWE value during baseline will be considered worsened sleep or wake fragmentation.

To assess rebound sleep and wake fragmentation, both categorical analysis at the subject level and continuous analysis at the group mean level will be performed. For each of the 2 weeks of the Follow-Up Period the proportion of subjects whose corresponding value for aSE or aWE exceeds the corresponding baseline value by 1% for aSE and 0.5% for aWE (which is approximately 5 minutes based on the a typical 8-hour sleep period and 16-hour wake period) 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, if deemed appropriate. (revised per Amendment 06)

To assess statistical significance using the continuous data at the group mean level, the data will be analyzed using ANCOVA, adjusted for country and treatment. The LS mean of each week of the Follow-Up Period will be compared to the baseline between each treatment group and placebo. If the upper bound of the 95% CI of aSE or aWE for the mean of each week of the Follow-Up Period is less than the lower bound of a 95% CI for the values during the baseline in

the given treatment group, it will be considered strong evidence for rebound sleep or wake fragmentation. If the LS means for aSE and aWE for the Follow-Up Period are all higher than for the baseline, then no rebound sleep or wake fragmentation 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 sleep and/or wake fragmentation is present.

Each domain of CGIC-ISWRD Scale at Day 29 will be analyzed using the Cochran–Mantel–Haenszel test, adjusted for country. (revised per Amendment 01)

The change from baseline of total score from the NPI-10, SDI, ADAS-Cog and MMSE at Day 29 will be analyzed with ANCOVA, with treatment and baseline as fixed effects on the Efficacy Analysis Set. The difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% confidence intervals (CIs) and p-values will be presented. (revised per Amendment 05)

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

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

A population PK approach will be used to characterize the PK of lemborexant. For this approach, PK 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 intrinsic and extrinsic factors (ie, demographics, concomitant medications) on the PK of lemborexant will be evaluated. The PK model will be parameterized for oral clearance (CL/F) and volume of distribution (V/F). Derived exposure parameters such as AUC, C_{max} and any other relevant parameters will be calculated from the model using the individual posterior estimate of CL/F and dosing history.

Baseline cognitive enhancer(s) plasma concentrations from appropriate subjects will be compared to those at end of treatment.

Further details of the PK analyses will be provided in a separate analysis plan.

9.7.1.7.2 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

All of the PD variables are considered efficacy variables for the purposes of analysis. (revised per Amendment 01)

9.7.1.7.3 PHARMACOKINETIC/EFFICACY ANALYSES

The relationship between exposure to lemborexant and efficacy variables including but not limited to SFI and WFI, and the most frequently occurring TEAEs, will be explored graphically. For modeling purposes, the change from baseline at the last week of treatment for the following efficacy variables aSE, aWE, SFI, WFI, IV, IS, AMP, and RA will be treated as PD variables.

Any emergent relationships will be evaluated by population PK/efficacy modeling. The population PK/efficacy analysis plan will be described and results will be reported in a separate document.

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

9.7.1.7.4 PHARMACOGENOMIC ANALYSES

DNA samples will be collected and stored, and may be used to examine the role of genetic variability in absorption, distribution, metabolism, and excretion, or development of AEs. Variations in lemborexant exposure or AEs may be explored by correlation of single-nucleotide polymorphisms with PK, safety, or efficacy data. Efficacy will be explored in relation to the APOε4 genotype.

9.7.1.8 Safety Analyses

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

9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized descriptively for lemborexant.

Compliance for lemborexant will be calculated on the basis of the number of tablets dispensed, lost, and returned, separately for each type (dose) of tablet. Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and greater than 120%.

9.7.1.8.2 ADVERSE EVENTS

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

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

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

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

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

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]). 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 that are characterized according to the customized MedDRA query PT as potential cataplexy-related events (Section 9.5.1.5), as seizure-related events, as well as somnolence and related events, and drug abuse liability will be summarized separately. (revised per Amendment 02)

9.7.1.8.3 CLINICAL LABORATORY VALUES

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

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

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

9.7.1.8.4 VITAL SIGNS AND WEIGHT

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from 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 (Table 4). Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented by treatment group and visit.

Table 4 Vital Sign Criteria

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

BP = blood pressure, bpm = beats per minute, H = high, L = low.

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from Baseline will be presented by treatment group. Shift tables will present changes from Baseline in ECG interpretation (categorized as normal or abnormal) by time point. (revised per Amendment 02)

For each subject, the maximum observed QTcF and the maximum prolongation from baseline in QTcF will be compiled. Categorical analyses of subjects (number and percent) with maximum observed QTcF values >450 msec, >480 msec, and >500 msec and maximum prolongations (from Baseline) in QTcF >30 msec and >60 msec will be presented by treatment group and by time point. Categorical analyses of subjects (number and percent) with maximum observed PR values >220 msec, and QRS values > 120 msec will be presented by treatment group and by time point. (revised per Amendment 01)

9.7.1.8.6 OTHER SAFETY ANALYSES (REVISED PER AMENDMENT 05)

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

9.7.1.9 Other Analyses

Endpoints may also be presented graphically or analyzed by modeling methods if warranted. (revised per Amendment 06)

The change from baseline of the EQ-5D-5L utility and VAS scores, the global score of PSQI, all scores of the ZBI-short and the SDI at Day 29 will be analyzed using ANCOVA, with treatment and baseline as fixed effects. Provided that the data are normally distributed, LS means, difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% confidence intervals (CIs) and p-values will be presented. The analyses for the EQ-5D-5L (caregiver self-version), PSQI, and ZBI will be conducted for a) caregivers who reside in the same residence as the subjects, b) caregiver informants who do not, reside in the same residence as the subjects, and c) all types of caregivers/informants combined. (revised per Amendment 01)

9.7.2 Determination of Sample Size (revised per Amendment 06)

Approximately 60 subjects will enroll in this proof-of- concept study. (revised per Amendment 06)

Some supporting exploratory power estimation is based on testing the dose response using the MCP-Mod package in R; several dose response curves were explored at one-sided 0.05 level of significance with different values of n (12, 13, and 14 subjects) per treatment group (Table 5, Table 6, and Table 7). (revised per Amendment 06)

Conservative scenarios based on a 10-percentage point difference between the active dose and placebo will be presented. (revised per Amendment 06)

Table 5 Power Calculations for Actigraph Sleep Efficiency Under Different Dose Response Curves (n=12 and sigma=12) (revised per Amendment 06)

Model (R variables)	Optimal Contrasts (PBO, 2.5, 5, 10, 15)	Power (%)
BetaMod 1 (0.339,0.05)	–0.82, –0.074, 0.116, 0.336, 0.442	0.6674254
BetaMod 2 (0.5,0.3)	–0.834, –0.073, 0.187, 0.414, 0.305	0.6588761
BetaMod 3 (0.19,0.15)	–0.887, 0.124, 0.236, 0.304, 0.223	0.6807728
E-max 1 (0.66)	–0.883, 0.095, 0.209, 0.277, 0.301	0.6953901
E-max 2 (1.1)	–0.869, 0.033, 0.195, 0.301, 0.340	0.6879214
E-max 3 (3)	–0.804, –0.123, 0.133, 0.349, 0.445	0.6782399
Exponential 1 (6.2)	–0.378, –0.319, –0.231, 0.097, 0.832	0.6843346
Exponential 2 (3)	–0.285, –0.274, –0.251, -0.071, 0.881	0.6890958
Linear[a]	–0.540, –0.332, –0.125, 0.291, 0.706	0.6830898
Linear-log (3.3)	–0.732, –0.210, 0.048, 0.351, 0.543	0.670295
Logistic 1 (0.13,0.732)	–0.892, 0.165, 0.241, 0.243, 0.243	0.714469
Logistic 2 (5,1)	–0.531, –0.459, –0.016, 0.500, 0.507	0.8027349
Logistic 3 (6,2)	–0.517, –0.399, –0.130, 0.460, 0.587	0.7642835
Quadratic (-0.029)	–0.643, –0.307, –0.023, 0.386, 0.586	0.6840342
SigEMax 1 (20.46,0.5)	–0.809, –0.093, 0.106, 0.329, 0.467	0.662415
SigEMax 2 (0.89,2.4)	–0.892, 0.162, 0.233, 0.247, 0.249	0.7117789

Table 6 Power Calculations for Actigraph Sleep Efficiency Under Different Dose-Response Curves (n=13 and sigma=12) (revised per Amendment 06)

Model (R variables)	Optimal Contrasts (PBO, 2.5, 5, 10, 15)	Power (%)
BetaMod 1 (0.339,0.05)	–0.82, –0.074, 0.116, 0.336, 0.442	0.6990587
BetaMod 2 (0.5,0.3)	–0.834, –0.073, 0.187, 0.414, 0.305	0.6908521
BetaMod 3 (0.19,0.15)	–0.887, 0.124, 0.236, 0.304, 0.223	0.7140683
E-max 1 (0.66)	–0.883, 0.095, 0.209, 0.277, 0.301	0.7286372
E-max 2 (1.1)	–0.869, 0.033, 0.195, 0.301, 0.340	0.7206645
E-max 3 (3)	–0.804, –0.123, 0.133, 0.349, 0.445	0.7098843
Exponential 1 (6.2)	–0.378, –0.319, –0.231, 0.097, 0.832	0.7170187
Exponential 2 (3)	–0.285, –0.274, –0.251, -0.071, 0.881	0.7225359
Linear[a]	–0.540, –0.332, –0.125, 0.291, 0.706	0.7148674
Linear-log (3.3)	–0.732, –0.210, 0.048, 0.351, 0.543	0.7011122
Logistic 1 (0.13,0.732)	–0.892, 0.165, 0.241, 0.243, 0.243	0.7477969
Logistic 2 (5,1)	–0.531, –0.459, –0.016, 0.500, 0.507	0.8321559
Logistic 3 (6,2)	–0.517, –0.399, –0.130, 0.460, 0.587	0.7948821
Quadratic (-0.029)	–0.643, –0.307, –0.023, 0.386, 0.586	0.7160553
SigEMax 1 (20.46,0.5)	–0.809, –0.093, 0.106, 0.329, 0.467	0.6949806
SigEMax 2 (0.89,2.4)	–0.892, 0.162, 0.233, 0.247, 0.249	0.7447213

Table 7 Power Calculations for Actigraph Sleep Efficiency Under Different Dose Response Curves (n=14 and sigma=12) (revised per Amendment 06)

Model (R variables)	Optimal Contrasts (PBO, 2.5, 5, 10, 15)	Power (%)
BetaMod 1 (0.339,0.05)	–0.82, –0.074, 0.116, 0.336, 0.442	0.7293262
BetaMod 2 (0.5,0.3)	–0.834, –0.073, 0.187, 0.414, 0.305	0.7217665
BetaMod 3 (0.19,0.15)	–0.887, 0.124, 0.236, 0.304, 0.223	0.7453197
E-max 1 (0.66)[a]	–0.883, 0.095, 0.209, 0.277, 0.301	0.7587574
E-max 2 (1.1)	–0.869, 0.033, 0.195, 0.301, 0.340	0.7508701
E-max 3 (3)	–0.804, –0.123, 0.133, 0.349, 0.445	0.7396949
Exponential 1 (6.2)	–0.378, –0.319, –0.231, 0.097, 0.832	0.7473776
Exponential 2 (3)	–0.285, –0.274, –0.251, -0.071, 0.881	0.7537709
Linear[a]	–0.540, –0.332, –0.125, 0.291, 0.706	0.7447648
Linear-log (3.3)	–0.732, –0.210, 0.048, 0.351, 0.543	0.7311277
Logistic 1 (0.13,0.732)	–0.892, 0.165, 0.241, 0.243, 0.243	0.7783044
Logistic 2 (5,1)	–0.531, –0.459, –0.016, 0.500, 0.507	0.8576103
Logistic 3 (6,2)	–0.517, –0.399, –0.130, 0.460, 0.587	0.8224386
Quadratic (-0.029)	–0.643, –0.307, –0.023, 0.386, 0.586	0.7454875
SigEMax 1 (20.46,0.5)	–0.809, –0.093, 0.106, 0.329, 0.467	0.725321
SigEMax 2 (0.89,2.4)	–0.892, 0.162, 0.233, 0.247, 0.249	0.7753528

9.7.3 Interim Analysis

A database lock will occur after all of the subjects have completed the Core Study, including the End of Study visit. The Core Study data will be analyzed according to the Core Study SAP. A second database lock will occur after the End of Study visits have been completed for the Extension Phase. Analyses for the Extension Phase will be based on the Extension Phase SAP. (revised per Amendment 05)

An interim analysis will be conducted with only the subjects from the US and Japan; details will be provided in the SAP. (revised per Amendments 05 and 06)

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/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 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 local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

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

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, (eg, ECGs, rhythm strips, electroencephalograms, polysomnographs, actigraphy) 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 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

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

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

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. Source data for actigraphy will be located at the central scoring vendor. The investigator agrees to allow direct access to source documents and study facilities to sponsor representatives, monitors and auditors and agree to inspection by regulatory authorities or IRB/IEC representative. (revised per Amendments 01 and 04)

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). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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

11.7 Auditing Procedures and Inspection

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

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

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission

pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

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

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

11.11 Discontinuation of Study

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

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

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values (revised per Amendment 03)

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)[a]	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values

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

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

[a] Please note that it is not required to measure fasting glucose in this protocol. (revised per Amendment 03)

Appendix 2 Pharmacogenomic Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacogenomic (PG) analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the PG samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PG analysis is not required, and will be obtained only from consenting subjects.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because

it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PG analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical

relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PG results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

Appendix 3 Prohibited Concomitant Medications

(revised per Amendments 03 and 06)

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)	-
Antidepressants with anticholinergic properties	-
Strong CYP3A inhibitors	• Amiodarone • Bocepravir • Clarithomycin • Cobicistat • Conivaptan • Diltiazem • Danoprevir • Eltegravir • Fluvoxamine • Grapefruit juice • Idelalisib • Indinavir • Itraconazole • Ketoconazole • Lopinavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telapravir • Telethromycin • Tipranavir • Troleandomycin • Voriconazole • (revised per Amendment 02)

Category	Medication
Moderate CYP3A inhibitors	• Amprenavir • Aprepitant • Atazanavir • Casopitant • Cimetidine • Ciprofloxacin • Clotrimazole • Crizotinib • Cyclosporin • Darunavir • Dronadarone • Erythromycin • Faldaprevir • Fluconazole • Fluvoxamine • Imatinib • Netupitant • Tofisopam • Verapamil (revised per Amendment 06)
CYP3A inducers	• Avasimibe • Bosentan • Carbamazepine • Efavirenz • Enzaluteamide • Etravirine • Lersivirine • Modafinil • Nafcillin • Phenobarbital • Phenytoin • Rifabutin • Rifampin • St. John's Wort • Talviraline • Troglitazone • Thioridazine (revised per Amendment 02)
Drugs that affect the circadian timing system	• Melatonin • Ramelteon • Tasimelteon
MAOIs	-
Opioid Analgesics	-

Category	Medication
Muscle relaxants (centrally-acting) with known sedating effects	• GABA analogues • Hydantoins • Phenyltriazines
Orexin receptor antagonists (revised per Amendment 05)	• Suvorexant
Other	• Warfarin, heparin, ticlopidine • Non-stimulant diet pills • Systemic isoretinoin • Systemic glucocorticoids • Tryptophan

GABA = gamma-aminobutyric acid, H1 = histamine type 1 receptor, MAOI = monoamine oxidase inhibitors

Appendix 4 Extension Phase

(revised per Amendments 05 and 06)

DESIGN AND PLAN

The Extension Phase comprises a 30-month Maintenance Period and a 14-day Follow-Up Period.

Subjects who complete the Core Study End of Study (EOS) Visit within 30 days prior to enrollment in the Extension Phase will be eligible for participation.

For subjects continuing directly from the Core Study to the Extension Phase, the End of Study (EOS) Visit of the Core Study will be the start of the Extension Phase.

Subjects who complete the Core Study, but who do not elect to immediately roll over to the Extension Phase will be required to return to the site within 30 days of completion of the Core Study and repeat selected assessments before being dispensed drug for the Extension Phase. If subjects return before 30 days of the last study visit, the tests that are required at that time are vital signs, weight, SDI, and eC-SSRS. All other data will be carried over from Visit 6A. If subjects return on Day 30, all tests listed for Visit 6B will be performed.

Maintenance Period

During the Maintenance Period, all subjects initially will receive lemborexant 10 mg per day (LEM10). At the discretion of the investigator, subjects will have the option of increasing the dose to lemborexant 15 mg per day (LEM15) or decreasing to lemborexant 5 mg per day (LEM5). All dose adjustments will be performed at an unscheduled visit or at the next scheduled visit. The dose can be adjusted more than once during the Extension Phase.

All doses will be taken orally in tablet form each night for the duration of the Extension Phase immediately (ie, within 5 minutes) before the time the subject intends to sleep. Subjects will receive 1 or 2 tablets as described below:

- LEM5: one lemborexant 5-mg tablet
- LEM10: one lemborexant 10-mg tablet
- LEM15: one lemborexant 5-mg tablet and one lemborexant 10-mg tablet

Study visits, either in person or by telephone, will be conducted according to the Schedule of Procedures and Assessments for the Extension Phase (Table 8). If the phone visit indicates an ongoing AE, the subject should be brought to the clinic for an Unscheduled Visit. Subjects may discontinue from study drug for any reason. A subject who prematurely discontinues taking study drug should return to the clinic within 2 weeks of discontinuation to complete an Early Termination Visit. The assessments of the Early Termination (ET) Visit are the same as those for the EOS Visit for the Core Study. If the subject discontinues

from the study due to an adverse event (AE), the subject must complete an ET Visit, and the AE must be followed to resolution for a period of 4 weeks, whichever comes sooner.

Follow-Up Period

The Follow-Up Period will be 14 to 18 days in duration and begins when subjects leave the clinic at the end of the Maintenance Period. Subjects and caregivers will return to the clinic at least 14 days but no more than 18 days after the end of the Maintenance Period for the End of Study Visit, including the recording of AEs and concomitant medications, and assessment of clinical laboratory tests, vital signs, and weight, and measurement of an electrocardiogram (ECG).

Treatment in the Extension Phase will last for a maximum duration of 30 months, until lemborexant is commercially available, or until the lemborexant clinical development program for Irregular Sleep-Wake Rhythm Disorder (ISWRD) is discontinued.

END OF EXTENSION PHASE

Estimates for End of the Extension Phase are as follows:

The End of the Extension Phase will be the date of the last study visit for the last subject in the Extension Phase.

Duration of Treatment: Up to 30 months, or until lemborexant is commercially available, or until the lemborexant clinical development program for ISWRD is discontinued.

INCLUSION CRITERIA

1. Completed the Core Study (EOS Visit). Subjects who participated in the Core Study and completed the EOS Visit within 30 days may return to participate in the Extension Phase as long as there are no contraindications due to ongoing AEs or prohibited medications.

EXTENSION PHASE ASSESSMENTS

Efficacy Assessments

The Sleep Disorders Inventory (SDI), completed by the caregiver as proxy for the subject, will be performed according to the Schedule of Procedures and Assessments (Table 8). The SDI is described in detail in Section 9.5.1.3.

Safety Assessments

Subjects will have routine safety assessments during the Extension Phase, including monitoring, questioning and recording of AEs, measurements for ECGs, vital signs, and weight, and blood and urine collection for clinical hematology and chemistry analysis, urinalysis, and electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Table 8)

Complete descriptions of all safety parameters are located in Section 9.5.1.5.

SCHEDULE OF PROCEDURES and ASSESSMENTS

Table 8 presents the Schedule of Procedures/Assessments for the Extension Phase.

Table 8 Schedule of Procedures and Assessments for Study E2006-G000-202 Extension Phase (revised per Amendment 06)

Phase	**Extension**																				
Period	**Maintenance**																			**FU**	
Visit Number[a]	**6B**[b]	**7**[c]	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**EOS/ ET 25**[d,e]	**UN**[f]
Study Day		**73**	**103**	**133**	**163**	**193**	**223**	**253**	**283**	**313**	**343**	**373**	**403**	**493**	**583**	**673**	**763**	**853**	**943**	**957**	
Procedures/ Assessments																					
Physical exam[g]	X	X	X	X			X			X			X	X	X	X	X	X	X	X	
Weight	X	X	X	X			X			X			X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X			X			X			X	X	X	X	X	X	X	X	
12-lead ECG	X			X			X			X			X	X	X	X	X	X	X	X	
Clinical laboratory tests	X			X			X			X			X	X	X	X	X	X	X	X	
SDI[h]	X			X			X			X			X	X	X	X	X	X	X	X	
eC-SSRS	X			X			X			X			X	X	X	X	X	X	X	X	
Phone call follow-up					X	X		X	X		X	X									
Dispense study drug[i]	X	X	X	X			X			X			X	X	X	X	X	X			X[i]
Retrieve unused study drug		X	X	X			X			X			X	X	X	X	X	X	X	X	
Study drug compliance		X	X	X			X			X			X	X	X	X	X	X	X		

Table 8 Schedule of Procedures and Assessments for Study E2006-G000-202 Extension Phase (revised per Amendment 06)

Phase	**Extension**																				
Period	**Maintenance**																			**FU**	
Visit Number[a]	**6B**[b]	**7**[c]	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**EOS/ ET 25**[d,e]	**UN**[f]
Study Day		**73**	**103**	**133**	**163**	**193**	**223**	**253**	**283**	**313**	**343**	**373**	**403**	**493**	**583**	**673**	**763**	**853**	**943**	**957**	
Procedures/ Assessments																					
Concomitant medications	---------->																				
Adverse events[j]	---------->																				

ECG = electrocardiogram, eC-SSRS = electronic Columbia-Suicide Severity Rating Scale, EOS = End of Study, ET = Early Termination, FU = Follow-Up, MCB = median calculated bedtime, SDI = Sleep Disorders Inventory, UN = Unscheduled Visit.

Table 8 Schedule of Procedures and Assessments for Study E2006-G000-202 Extension Phase (revised per Amendment 06)

Phase	Extension																				
Period	Maintenance																			FU	
Visit Number[a]	6B[b]	7[c]	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	EOS/ ET 25[d,e]	UN[f]
Study Day		73	103	133	163	193	223	253	283	313	343	373	403	493	583	673	763	853	943	957	
Procedures/ Assessments																					

a: Visits 7, 8, and 9 to be conducted within a window of ±3 days of the scheduled visit day. Visit 10 through Visit 24 to be conducted within a window of ±7 days of the scheduled visit day. (revised per Amendment 06)

b: For subjects who enter directly into the Extension Phase, the End of the Study (EOS) Visit for the Core Study is the first visit in the Extension Phase. Subjects may enter the Extension Phase up to 30 days after the EOS Visit of the Core Study (see Schedule of Assessments and Procedures for the Core Study); these subjects are required to have the following evaluations at study enrollment: vital signs, weight, SDI, and eC-SSRS. Subjects who enroll in the Extension Phase the 30th day following the EOS Visit, must repeat the EOS Visit assessments at the time of enrollment (at Visit 6B). (revised per Amendment 06)

c: Visit 7 should be up to and including 30 days after Visit 6B if the subject does not enter directly. The days between Visit 6A and 6B are not included in the calculation of study days. (revised per Amendment 06)

d: Visit 25 occurs at least 14 days but no more than 18 days after the Visit 24.

e: Subjects who discontinue the study early for any reason should complete the Early Termination (ET) Visit.

f: In case of dose adjustment, the subject will need to come for an Unscheduled Visit (UN), or have the adjustment made at a scheduled clinic visit. Additional assessments may be conducted at the Unscheduled Visit if the investigator considers them to be necessary.

g: A full physical examination will be conducted at Visit 6B for subjects with a >30-day gap before enrollment into the Extension Phase) and at the End of Study Visit for the Extension Phase; an abbreviated physical examination will be conducted at all other visits. (revised per Amendment 06)

h: The Sleep Disorders Inventory (SDI) will be completed by the caregiver as proxy for the subject.

i: Drug will be dispensed to caregivers who will administer study drug to subjects. All study drug administration must be within 5 minutes of bedtime (defined as the time the subject attempts to sleep). (revised per Amendment 06)

j: 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.

EXTENSION PHASE STATISTICAL METHODS

Endpoints

Efficacy Endpoint

The efficacy endpoint is the change from baseline in SDI total score.

Safety Endpoint

The safety endpoints are:

- Safety and tolerability of lemborexant, including AEs and serious adverse events (SAEs).
- eC-SSRS

Definitions of Analysis Sets

- Safety Analysis Set: the group of Extension Phase subjects who received at least 1 dose of Treatment Phase study drug and had at least 1 postdose safety assessment
- The Full Analysis Set (FAS): the group of subjects who received at least 1 dose of study drug and had at least 1 postdose measurement in the Extension Phase

Statistical Analyses

All statistical analyses will be performed using Statistical Analysis Software (SAS) or other validated statistical software. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

Efficacy Analysis

The change from Baseline of the scale domains, as well as total score from the efficacy endpoint SDI will be summarized by time point and by modal dose.

Other comparisons may be performed as appropriate in the future (subjects who remain on LEM10 and never switch vs subjects who switch from LEM10), and these will be included in the Extension Phase SAP.

Safety Analysis

The analysis of safety data will be performed by time point and modal dose. Other comparisons may be performed if appropriate and these will be included in the Extension Phase SAP.

The safety endpoints of adverse events (treatment-emergent adverse events [TEAEs], SAEs, and AEs leading to discontinuation) will be summarized by System Organ Class (SOC) and Preferred Term (PT), and the incidence of AEs will be summarized by maximum severity and relationship to study drug. Change from baseline analyses will be presented for clinical laboratory values, vital signs and weight, ECGs, and physical examination results. The results of eC-SSRS assessments will be listed for each subject, and the incidence of treatment-emergent suicidal ideation or suicidal behavior will be summarized by treatment group as above using descriptive statistics.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2006-G000-202

Study Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia (revised per Amendment 05)

Investigational Product Name: lemborexant

IND Number: 130798

EudraCT Number: 2017-003306-40 (revised per Amendment 05)

SIGNATURES

Authors: (revised per Amendments 02 and 04)

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Date

Neuroscience Business Group
Eisai Inc. (revised per Amendment 06)

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2006-G000-202
Study Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of the Efficacy and Safety of Lemborexant in Subjects with Irregular Sleep-Wake Rhythm Disorder and Mild to Moderate Alzheimer's Disease Dementia (revised per Amendment 05)
Investigational Product Name:	lemborexant
IND Number:	130798
EudraCT Number:	2017-003306-40 (revised per Amendment 05)

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

Medical Institution

Investigator	Signature	Date
PPD		
PPD	Signature	Date

Medicine Development Center
Eisai Co., Ltd.