2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lemborexant oral tablets	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Lemborexant	Volume: Page:	

Study 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

Investigators/Sites

Stephen Thein, PhD (Principal Investigator), et al.
Multicenter: 47 sites in the United States (US), 9 sites in Japan, and 1 site in the United Kingdom (UK).
(refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None

Study Period

20 Dec 2016 (date of first subject's signed informed consent) to 26 Jul 2018 (date of last subject's last visit/assessment in the Core Study)

Phase of Development

Phase 2

Objectives

Sleep-Related Objectives

- 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 Irregular Sleep-Wake Rhythm Disorder (ISWRD) and Alzheimer's disease dementia (AD-D).
- 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.
- 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.
- To determine the change from baseline of the mean duration of wake bouts (aMeanDurWB) over each week of treatment.

Wake-Related Objectives

- To determine the dose response of LEM2.5, LEM5, LEM10, and LEM15 compared to PBO on the change from baseline in actigraphy-derived Wake Efficiency (aWE) during the last week of treatment in subjects with ISWRD and AD-D.
- To determine the efficacy of LEM2.5, LEM5, LEM10, and LEM15 compared to PBO on the change from baseline of aWE during each week of treatment.
- To determine the efficacy of 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.

- To determine the change from baseline of the mean duration of sleep bouts (aMeanDurSB) over each week of treatment.

Circadian Rhythm-Related Objective

- 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

Additional Objectives

- 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
  - 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 (ZBI)-short form.
  - Change from baseline of health outcomes of the subject and/or caregiver on the EuroQOL version 5 dimensions, 5 levels (EQ-5D-5L) (subject Self Version, caregiver Self Version, caregiver proxy for the subject [Proxy 1 Version]).
  - Change from baseline of Mood and behavior on the Neuropsychiatric Inventory-10 item version (NPI-10; by caregiver as proxy for the subject).
  - Change from baseline of the Sleep Disorders Inventory (SDI; 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. [Note: this objective is for the Extension Phase and will be presented in a separate report]

Methodology

E2006-G000-202 was 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 complained of disrupted sleep or multiple awakenings at night along with frequent periods of falling asleep during the day that impacted the quality of life of the subject. For each subject, an individual who knew the subject well and would provide the information about themselves were also enrolled in the study (see Caregivers and Informants, below). Additional informants may also have been

associated with the study but were not required to complete a consent form.

The study had 3 phases: the Prerandomization Phase, the Randomization Phase, and the Extension Phase. This clinical study report (CSR) only reports the Core Study including the Prerandomization and Randomization Phases, and the Extension Phase will be described in a separate CSR.

Prerandomization Phase

There were circumstances where the subject and/or caregiver was not sure whether the subject had an ISWRD sleep/wake pattern, 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 were allowed to offer the subject an opportunity to wear a designated activity tracker before consenting to the rest of the study procedures.

The duration of the Screening Period was to be up to 42 days. At the first visit, informed consent was obtained after the study had been fully explained to each subject and caregiver and before the conduct of any screening procedures or assessments. Subjects or their legal representative signed the informed consent; and caregivers had to sign a separate consent form. The clinician was required to confirm that the subject met diagnostic criteria for AD-D, based on the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines. If documentation of the Alzheimer's disease (AD) diagnosis was not available, investigators were allowed to 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 was conducted, and included confirmation that the subject met diagnostic criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type. Subjects were administered the MMSE and the electronic version of the Columbia–Suicide Severity Rating Scale (eC-SSRS), and underwent the subject component of the Cornell Scale for Depression in Dementia (CSDD) interview. Additional eligibility criteria were evaluated and clinical laboratory tests, electrocardiogram (ECG), vital signs, height, weight, and viral screening were assessed. Caregivers were administered the caregiver input component of the CSDD.

Eligible subjects were provided with an actigraph (for actigraphy) to wear continuously for at least the first 14 days of screening. They were asked to provide a typical (habitual) time when the subject went to sleep at night.

The appropriate informants were provided with a daily log (sleep period log) to note the start and end times of the subject's actual time in bed (TIB) 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 were trained in the use of the actigraph and the log. Site staff instructed 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 emphasized the importance of doing so. Sites also arranged 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 had been obtained within the previous 6 months. Before randomization, the investigator was required to review a report detailing the subject's apnea-hypopnea index (AHI).

After subjects had worn the actigraph for at least 14 days, caregivers returned to the clinic. The actigraph data were downloaded and transmitted to the central reader along with the sleep log of bedtimes, morning waketimes, and times when the actigraph was replaced on the subject's wrist. Adverse events (AEs) and concomitant medication use were recorded. The sites kept the actigraph at the clinic until the Baseline visit, when the same device was again provided to the subjects. The central scoring determined whether the data from the screening period met the quality standards required by the inclusion criteria.

During the Screening Period, subjects who met the eligibility criteria for ISWRD on the basis of actigraphy and were not excluded on the basis of the diagnostic sleep study for sleep apnea were then scheduled for the Baseline visit. Subjects who did not meet eligibility criteria based on actigraphy were allowed to be rescreened, following consultation with the Sponsor, as long as they were not excluded based on AHI.

On Day 1, the Screening Period ended and the Baseline Period started. The Baseline visit had to occur no earlier than 2 days and no later than 27 days after Visit 2 (caregiver visit), and was allowed to be scheduled across 2 consecutive days if necessary. Physical examinations, clinical laboratory tests, an ECG, vital signs, AEs, concomitant medications, and weight were assessed. The site on the arm where the actigraph was applied was examined. A plasma sample was obtained from any subject taking any cognitive enhancer(s) and was used to

measure plasma concentrations of the enhancer(s). As proxy for the subject, caregivers completed the SDI, NPI-10 and the EQ-5D-5L (Proxy Version 1). The caregiver also completed the EQ-5D-5L, ZBI-short form, and the PSQI for himself/herself. The subject was administered the ADAS-cog and the EQ-5D-5L (Self version). The rater completed the baseline assessment for the CGIC-ISWRD Scale.

Randomization Phase

The Treatment Period began on the evening of Day 1 and continued for 4 weeks. Subjects were randomized, in a double-blind manner, to receive LEM2.5, LEM5, LEM10, LEM15, or PBO. Study drug was dispensed to the caregiver. During the Treatment Period, subjects were to receive 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). Prior to the implementation of Protocol Amendment 05, subjects received study drug each night immediately (ie, within 5 minutes) before bedtime (defined as the time the subject intended to try to fall asleep). Time of dosing was collected on the sleep log and entered by the sites into the appropriate electronic case report form (eCRF), starting with Amendment 05.

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

If the subject experienced an AE that resulted in a temporary discontinuation of study medication, a rechallenge was allowed following consultation with the Medical Monitor.

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

During the End of Treatment visit, the study staff discussed details about the Extension Phase with potentially eligible subjects and caregivers.

The Follow-Up Period began when subjects left the clinic at the end of the Treatment Period. Subjects ceased taking study drug but continued to wear the actigraph until the End of Study (EOS) Visit.

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

A subject who prematurely discontinued taking study drug was supposed to 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 discontinued from the study due to an AE, the subject had to complete an Early Termination Visit, and the AE had to be followed to resolution or for 2 weeks, whichever came sooner.

The estimated duration for each subject in the Core Study was 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 EOS visit]).

Caregivers and Informants

For the subject to enroll, there had to be 1 or more persons responsible to provide the required information for assessments, complete the sleep log for actigraphy, and ensure that the subject was dosed at the appropriate time. These roles were allowed to be fulfilled by the same or different individuals. For each subject, one individual was designated as the "caregiver informant" (or "caregiver"), who was 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 was required to spend at least 10 hours per week with the subject.

If the caregiver informant did not reside with the patient, then the other informant(s) was responsible for ensuring that the sleep log was completed daily and that dosing occurred at the appropriate time. There could 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 was to be replaced by a suitable alternate until the Baseline Visit, and thereafter only following consultation with the Sponsor.

Adjudication Committee

An independent Adjudication Committee was employed at intervals to review, in a blinded manner, AEs that could potentially be considered cataplexy or seizure. A set of preferred terms (PTs) constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure were 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 were instructed to query subjects and their caregivers who reported any of the above events for supplemental information about events using a questionnaire for events potentially related to cataplexy and the serious adverse event (SAE) form for any of the above events considered serious.

There were no events that needed to be adjudicated in the Core Study.

Number of Subjects (Planned and Enrolled)

Planned: approximately 60 subjects were to be randomized to each of the 5 treatment groups (12 subjects in each treatment group).

Screened: 214 subjects (including 14 subjects who rescreened once and 1 subject who rescreened twice)

Randomized: 63 subjects (12, 12, 14, 13, and 14 subjects in PBO, LEM2.5, LEM5, LEM10, and LEM15 groups)

Treated: 62 subjects (12, 12, 13, 13, and 14 subjects in PBO, LEM2.5, LEM5, LEM10, and LEM15 groups)

Diagnosis and Main Criteria for Inclusion

Diagnosis

Irregular Sleep-Wake Rhythm Disorder

Key Inclusion Criteria for Subjects

Key inclusion criteria are briefly summarized as follows:

- Male or female, age 60 to 90 years at the time of informed consent
- Documentation of diagnosis with AD-D on the basis of the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines
- MMSE 10 to 26 at Screening
- Met criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (Diagnostic and Statistical Manual of Mental Disorders 5th edition [DSM-5]) and the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (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
- During the Screening Period, mean aSE <87.5% within the defined nocturnal sleep period and mean aWE <87.5% during the defined wake period

- 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-hour period, ≥3 days per week
- Had a reliable and competent caregiver (or caregiver and informants) who was able to accompany the subject to study visits, administer study medication on a nightly basis and provide information on the status of the subject

Key Exclusion Criteria for Subjects

Key exclusion criteria are briefly summarized as follows:

- A diagnosis of vascular dementia, dementia following multiple strokes, or any synucleinopathy/Lewy body disorder. This included dementia with Lewy bodies and Parkinson's disease with or without dementia.
- 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
- An apnea-hypopnea index (AHI) or equivalent ≥15 events/hour on diagnostic sleep study conducted prior to Baseline or within 6 months of Screening
- A clinically significant movement disorder that would affect the differentiation of sleep and wake by the actigraphy analytic algorithm
- Current symptoms or history during the past year of rapid eye movement (REM) behavior disorder or sleep-related violent behavior

Test Treatment, Dose, Mode of Administration, and Batch Numbers

The sponsor provided lemborexant tablets in strengths of 2.5 mg, 5 mg, and 10 mg. All subjects received 2 tablets as described below, at night immediately (ie, 5 minutes) before bedtime (defined as the median calculated bedtime [MCB], calculated based on the sleep log during Screening). Prior to the implementation of Amendment 05, subjects received study drug each night immediately (ie, within 5 minutes) before bedtime (defined as the time the subject intended to try to fall asleep).

- 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

Batch numbers:

Lemborexant 2.5-mg tablet: 110253

Lemborexant 5-mg tablet: 110254

Lemborexant 10-mg tablet: 110255

Reference Therapy, Dose, Mode of Administration, and Batch Number

The sponsor provided lemborexant-matched placebo tablets, identical in appearance.

Batch number: 110252

Duration of Treatment

Prerandomization Phase (Screening and Baseline Periods): up to a maximum of 42 days

Randomization Phase-Treatment Period: 28 days (4 weeks), subjects were received the study drug each night.

Randomization Phase-Follow-Up Period: a minimum of 14 days

Assessments

Efficacy

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 can be fitted to an algorithm from which rest/activity patterns can be derived.

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

Also noted that the calculated MCB determined time of dosing for a given subject such that the dose each night was required to be taken within 5 minutes before bedtime.

Actigraphy parameters were as follows:

- Actigraphy sleep efficiency (aSE): 100%×the total duration of sleep epochs during the predefined 8-hour nocturnal sleep period divided by 8 hours.
- Sleep fragmentation index (SFI) from actigraphy: the SFI were 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.
- Wake fragmentation index (WFI) from actigraphy: the WFI were 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.
- Actigraphy 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.
- 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 occurred during the defined nocturnal predefined sleep period.
- 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 occurred during the 16 hours outside of the predefined nocturnal sleep period.
- 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

The CGIC-ISWRD scale uses the standardized methodology for obtaining global clinical ratings, and was an assessment conducted by an independent rater at the end of the Treatment Period who had no access to post-baseline source data or other psychometric test scores conducted as part of the protocol. The instrument consisted 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 had to be a person who knew the subject well. The baseline interview served as a reference for future ratings. During the baseline interview, the rater evaluated 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 was used, from 1 = marked improvement, 4 = no change, to 7 = marked worsening, to score each of the 4 domains and to provide an overall score. The overall score was used to address the secondary objective; the domain scores were exploratory. In this study, the assessment focused on the symptoms of ISWRD, not the general condition of dementia.

Neuropsychiatric Inventory (NPI-10)

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 took 10 minutes for a clinician to administer. This scale was administered with the caregiver as proxy for the subject. The NPI-10 has good psychometric properties and is widely used in drug trials. The NPI-10 total score is derived by summing the products of the frequency and severity ratings for each area (range: 0–120 [worst]).

Mini Mental State Examination (MMSE)

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 were administered to the subject by site staff.

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

The ADAS-cog (Rosen et al., 1984) is the most widely used cognitive scale in AD 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, and number cancellation are also obtained. The modified version (ADAS-cog-13) used in this study was scored from 0 to 85 points with a score of 0 indicating no impairment, and a score of 85 indicating maximum impairment.

Sleep Disorders Inventory (SDI)

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 7 subquestions relating to sleep from the NPI sleep disturbance item. Each of the subquestions was 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. The SDI score was derived as the product of the average of the frequency ratings and the average of the severity ratings (range: 0–12 [worst]).

Pharmacokinetics

A blood sample for plasma concentrations of lemborexant and its metabolites M4, M9, and M10 was 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 were documented.

One blood sample (approximately 4 mL) was 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) was obtained at Visit 5 or Early Termination Visit for all subjects to measure lemborexant and its metabolites, as well as cognitive enhancers, as appropriate.

For those subjects taking donepezil, the date and time of the 2 most recent doses of donepezil were documented. For all subjects taking lemborexant, the date and time of the 2 most recent doses of lemborexant were also 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) was taken from the subject.

Pharmacokinetics/Pharmacodynamics

For PK/PD (exposure-response [E-R]) modeling purposes, efficacy variables including aSE, aWE, SFI, mean duration of sleep bouts, mean duration of wake bouts, RA, L5, and total sleep time (TST) were treated as PD variables.

Pharmacogenomics

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

Safety

Safety assessments consisted of monitoring, questioning, and recording all AEs and SAEs; periodic measurement of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight, and ECGs; and suicidality, assessed using the eC-SSRS.

Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

Suicidality was assessed using an electronic version of the C-SSRS. The eC-SSRS assessed an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Qualified personnel was required to 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 and number of bouts >10 minutes of sleep from the first 3 hours after waketime from the first 3 days of the first week of treatment and the last 3 days of treatment were compared with the mean activity levels and number of bouts >10 minutes of sleep from the first 3 hours after waketime during the actigraphy baseline period.

Other

Cornell Scale for Depression in Dementia (CSDD; only at Screening)

The CSDD derived information from the patient and the informant (caregiver) to assess signs and symptoms of major depression in patients with dementia. Information was elicited through 2 semi-structured interviews; an interview with an informant and an interview with the patient, both of which focused on depressive symptoms and signs that occurred during the week preceding the interview. The final ratings of the CSDD items represented the rater's clinical impression rather that the responses of the informant or the patient. The CSDD, which took approximately 20 minutes to administer, assessed 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 was rated for severity on a scale of 0 to 2 (0 = absent, 1 = mild or intermittent, 2 = severe). The item scores were added. Scores above 10 indicated a probable major depression. Scores above 18 indicated a definite major depression. Scores below 6 were associated with absence of significant depressive symptoms.

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 instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale (VAS) from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

Three forms were collected per subject per visit:

- Subject Self Version
  - The form was not labeled Self Version but the wording was for self-completion.
  - Caregivers or study coordinators could provide assisted self-completion services to the subject where the subject had physical impairments (eg, arthritis, severe visual impairment) that prevent self-completion. Assistance could be in the form of reading the instructions, questions, and responses verbatim (without interpretation) and in the order provided on the questionnaire. Assistance could be in the form of recording responses of the subject.
  - To be considered self-completed, all responses had to have come from the subject.
- Caregiver Self Version
  - The caregiver completed the standard version regarding his/her own health status.
  - Study coordinators were allowed to provide assisted self-completion services as described above for physically impaired caregivers.
- Caregiver Proxy 1 Version
  - During the Core Study only, the caregiver completed 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 were allowed to provide assisted self-completion services as described above for physically impaired caregivers.

Zarit Burden Interview (ZBI)–short form

The ZBI–short form was developed from the full ZBI, to be suitable for caregivers of cognitively impaired older adults across diagnostic groups. 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 could be completed by caregivers directly or as part of an interview of the caregiver by the study coordinator. Caregivers were 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.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is an instrument used to measure the quality and patterns of sleep in adults by measuring 7 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, 7 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. For this study, the PSQI was administered to the caregiver for self-completion.

Bioanalytical Methods

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

Statistical Methods

All statistical tests were based on the 5% level of significance (2-sided), unless otherwise stated. No multiplicity adjustments were made.

Study Endpoints

Sleep-Related Endpoints

The sleep-related endpoints were:

- The change from baseline of mean aSE with lemborexant compared to PBO during each week of treatment
- Change from baseline in mean SFI during each week of treatment
- Change from baseline of the aMeanDurWB during each week of treatment

Wake-Related Endpoints

The wake-related endpoints were:

- The change from baseline of mean aWE with lemborexant compared to PBO during each week of treatment
- Change from baseline of mean WFI during each week of treatment
- Change from baseline of the aMeanDurSB during each week of treatment

Circadian Rhythm-Related Endpoint

The circadian rhythm-related endpoints were:

- Change from baseline of IV, IS, L5, M10, AMP, and RA over each week of treatment

Additional Endpoints

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

- Safety and tolerability of lemborexant, including AEs and SAEs
- CGIC-ISWRD scale on symptoms of ISWRD total score and domains
- 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
- 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
- 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
- Change from baseline on the EQ-5D-5L utility and 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 population approach and descriptive statistics for the plasma concentrations of its metabolites M4, M9, and M10
- 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

Definitions of Analysis Sets

The Safety Analysis Set was 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) was 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 was the group of subjects who had at least 1 quantifiable plasma concentration of lemborexant, with adequately documented dosing history.

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

Efficacy Analyses

Efficacy Analyses for the Sleep-Related, Wake-Related, and Circadian Rhythm-Related Endpoints

The change from baseline of the mean aSE and mean aWE (separately) for the last 7 nights/days on treatment were analyzed using MCP-MOD (multiple comparisons and modelling) approach. Dose-response models that were evaluated were linear, linear log, quadratic, exponential, e_{max}, sigmoid e_{max}, beta, and logistic.

For all actigraphy parameters, baseline was defined as the average value of the last 7 days of Screening. For IS, IV, RA, AMP, L5, and M10 parameters, the weekly averages were calculated by actigraphy vendor. For these variables, the last record of Screening Period was considered as the baseline (the average of the last 7 days) of Screening Period.

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

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

The *P* value and Akaike Information Criteria for the trend test were reported for all models explored for the MCP-step. The dose response and target dose estimation for the chosen model were reported for the Mod-step.

The change from baseline of the following endpoints was analyzed using mixed models for repeated measures (MMRM) model 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. The model included all data and was 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 was used to construct the treatment comparisons at a specific time. The MMRM model accounted for any missing data, and assumed that the missing data were missing at random. An unstructured covariance matrix was used, and if the model failed to converge, then an autoregressive matrix was used. Where data were 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 were presented.

The mean aSE and aWE change from baseline were analyzed using the MMRM. The linear LSs were performed on aSE and aWE change from baseline at Week 1, Week 2, Week 3, and Week 4 of treatment on the FAS for LEM2.5, LEM5, LEM10, and LEM15 compared to PBO, where the model was explored with baseline

value, country and treatment as covariates/factors, and with and without age and MMSE score as further exploratory covariates. LS means, difference in LS means of each lemborexant dose compared to PBO, 95% CIs and *P* values at the appropriate time point were presented.

Efficacy Analyses for Additional Endpoints

The overall score of CGIC-ISWRD scale at Day 29 was analyzed using the Cochran-Mantel-Haenszel test, adjusted for country if data allow. Each domain of CGIC-ISWRD Scale and the total score at Day 29 were analyzed using the Cochran-Mantel-Haenszel test, adjusted for country if data allow.

Rebound sleep and wake fragmentation was defined as worsened aSE or aWE compared to baseline after study drug treatment was discontinued. Actigraphy data from the Follow-Up Period were 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 were 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 were performed. For each of the 2 weeks of the Follow-Up Period the proportion of subjects whose corresponding value for aSE or aWE was less than the corresponding baseline value by 5% for aSE and 1% for aWE (which is approximately minutes based on the a typical 8-hour sleep period and 16-hour wake period) were summarized by treatment group and compared to PBO. The percentage of 'rebounders' between each treatment and PBO was 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 were analyzed using ANCOVA, adjusted for country. The LS mean of each week of the Follow-Up Period were compared to the baseline between each treatment group and PBO. If the upper bound of the 95% CI of aSE or aWE for the mean of each week of the Follow-Up Period was less than the lower bound of a 95% CI for the values during the baseline in the given treatment group, it was to be considered strong evidence for rebound sleep or wake fragmentation. If the LS means for aSE and aWE for the Follow-Up Period were all higher than for the baseline, then no rebound sleep or wake fragmentation was suggested. Otherwise, the degree to which the parameters worsen, and the time point(s) at which they worsen were considered to evaluate whether clinically meaningful rebound sleep and/or wake fragmentation was present.

The change from baseline of total score from the NPI-10, SDI, ADAS-cog and MMSE at Day 29 was 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 were presented.

Pharmacokinetic Analyses

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

PK data from available Phase 1 and Phase 2 studies were pooled with data from this study for an assessment of exposures using a population PK approach. Due to the available sample size and the number of samples per subject, only between-study differences in oral clearance (CL/F) for Study 202 versus Phase 1 and Phase 2 studies were assessed. Subject-level PK model parameters were used to derive steady state average concentrations at ($C_{ave,ss}$) for subsequent E-R assessments.

Lemborexant 2- and 3-compartment population PK models with mixed absorption (zero and first order) were used to re-estimate the PK in the presence of data from this study. Only the lemborexant oral clearance (CL/F) parameter was allowed to be adjusted for data from this study. Other PK parameters were assumed to be common across all lemborexant studies. This updated model was used to predict individual-level lemborexant steady-state concentrations ($C_{ave,ss}$) in subjects with ISWRD and AD-D.

Baseline cognitive enhancer(s) plasma concentrations from applicable subjects were compared to those at the end of treatment.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacodynamic Analysis

All of the PD variables were considered efficacy variables for the purposes of analysis.

Pharmacogenomic Analyses

DNA samples were collected and stored, and might 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 might be explored by correlation of single-nucleotide polymorphisms with PK, safety, or efficacy data.

Pharmacokinetic/Pharmacodynamics (Exposure-Response [E-R]) Analyses

PK/PD analyses focused on the relationship of lemborexant exposure versus change from baseline in sleep, wake, and circadian rhythm endpoints: aSE, aWE, SFI, mean duration of sleep bouts, mean duration of wake bouts, RA, L5, and TST.

Plots of lemborexant exposure ($C_{ave,ss}$) versus response were evaluated using all available data, with each endpoint considered on the measurement scale or as change from baseline. Plots were also created to examine E-R for Week 1 and Week 4 independently. Linear regression analyses were used to evaluate the E-R data given the sparse PK and PD assessments of the study and the shape of the observed PK/PD relationship. Details of the population PK analyses and exposure/efficacy analyses are included in a population analysis report (CPMS-E2006-006R).

Exposure-response analyses of safety endpoints were not conducted due to the low incidence of events. Data from this study may be pooled with TEAE data from other lemborexant studies.

Safety Analyses

Evaluations of safety were 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 signs, and weight measurements, were summarized by treatment group using descriptive statistics.

The number (percentage) of subjects with TEAEs of cataplexy that were characterized according to the customized MedDRA query PT as potential cataplexy-related events or as seizure-related events was summarized separately. Adjudicated events were also presented separately.

To assess residual morning sleepiness levels, change from baseline in the sum of activity counts in the 3 hour interval after morning waketime was compared for each treatment group relative to PBO for each of the 6 mornings comprising the first 3 days and last 3 days of treatment. The change from baseline was 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 were presented. In addition, the change from baseline of the number of bouts >10 min scored as sleep was determined. The change from baseline was analyzed using ANCOVA, as above.

Other Analyses

Endpoints were also to be presented graphically or analyzed by modeling methods if warranted.

The change from baseline of the EQ-5D-5L utility and VAS scores, the global score of PSQI, all scores of the ZBI-short form and the SDI at Day 29 were analyzed using ANCOVA, with treatment and baseline as fixed effects. Provided that the data were normally distributed, LS means, difference in LS means of LEM2.5, LEM5, LEM10 and LEM15 compared to PBO, 95% CIs and P values were presented.

For the PSQI, caregivers who did not attend to the subject in the night were not included in the summaries and analysis. Caregiver data were not included in analyses if they did not live in the same dwelling as the subject.

Results

Subject Disposition/Analysis Sets

Of the 63 subjects randomized into the study, 1 subject in the LEM5 group was inadvertently given a randomization number but did not receive any study drug, and was therefore excluded from all analysis sets. A total of 50 subjects in the lemborexant dose groups (12, 13, 13, and 12 subjects in the LEM2.5, LEM5, LEM10,

and LEM15 groups, respectively) and 12 subjects in the placebo group received at least 1 dose of study drug, and all 62 treated-subjects completed the planned treatment regimen in the Core Study.

All 62 treated subjects were included in both the Safety and Full Analysis Sets. All lemborexant-treated subjects were included in the PK Analysis Set except for 1 subject in the LEM2.5 group for whom the PK sample was not collected at Visit 5.

Demographics

The treatment groups were generally balanced with respect to demographic variables across the 5 groups, although numbers of males versus females were not fully balanced among the groups (female percentage was 83.3% in the LEM15 group versus 46.2% to 61.5% in the other 4 groups). Overall, lemborexant-treated subjects and placebo-treated subjects were similar in age (mean age: 74.3 and 75.3 years, respectively), sex (female: 60.0% and 58.3%, respectively), weight (69.42 and 81.89 kg, respectively), and body mass index (BMI) (26.82 and 29.34 kg/m^2, respectively). Median AHI was between 3.60 and 7.05 events/hour among the 5 treatment groups, indicating many subjects had mild sleep apnea (ie, >5 and <15 events/hour). Genotyping of apolipoprotein E was conducted in 53 subjects overall; 3 subjects had 2 copies of the E4 allele and 14 subjects had 1 copy.

The actigraphy baseline variables were comparable across the 5 groups. SFI baseline means (50.07 to 58.51) and WFI baseline means (85.72 to 94.76) based on the logged time were comparable within the 5 groups. Also, aSE baseline means (76.34% to 78.45%) and aWE baseline means (67.19% to 72.53%) based on the logged time were also comparable within the 5 groups. The baseline actigraphy characteristics were consistent with the presence of ISWRD.

Mean MMSE score (19.8 to 22.2) was comparable within the 5 treatment groups and indicated mild to moderate AD. Mean ADAS-cog was slightly lower (less impaired) in the LEM5 group (26.97) than in the other groups (28.88 to 30.69).

Overall, the relationship of caregiver to subjects was a daughter in 16 subjects, followed by a wife in 15 subjects, and husband and friend/companion in 11 subjects each. Most caregivers were sleeping in the same room as the subjects (24 caregivers) or in an adjacent room to the subjects (17 caregivers).

Efficacy

Considering the exploratory nature of this proof-of-concept study with a limited number of subjects, the following descriptions are focused on numerical changes for summary statistics and the clinical significance. The following actigraphy data were calculated based on the actual (logged) TIB/time out of bed (TOB).

The compliance rate was between 80% and 120% in all treated subjects, indicating adequate treatment for pilot efficacy analyses for the Core Study.

Sleep-related endpoints

Actigraphy sleep efficiency (aSE): The changes from baseline of the mean aSE for the last week on treatment were analyzed using MCP-MOD approach, but no models showed a statistically significant trend. Mean baseline aSE values were 76.34% to 78.45% across all groups. LS mean differences (95% CI) from baseline compared to PBO were 3.177 (–0.741, 7.096), 2.802 (–1.119, 6.723), –0.960 (–4.777, 2.857), and 0.713 (–3.160, 4.585) percentage points (higher values indicate better sleep efficiency) for LEM2.5, LEM5, LEM10, and LEM15, respectively. Increased sleep efficiency during the night was generally observed for LEM2.5 and LEM5 across 4 weeks of treatment.

Sleep fragmentation index (SFI): Mean baseline SFI values were 50.07 to 58.51 across all groups. LS mean differences (95% CI) from baseline compared to PBO were –5.098 (–12.240, 2.045), –6.105 (–13.332, 1.122), 0.680 (–6.262, 7.623), and –3.140 (–10.178, 3.897) (lower values indicate more consolidated sleep during the night) for LEM2.5, LEM5, LEM10, and LEM15, respectively. More consolidated sleep during the night was consistently observed for LEM2.5, LEM5, and LEM15 across 4 weeks of treatment.

Mean duration of wake bouts: Mean baseline values were 20.32 to 21.94 across all groups. LS mean differences from baseline compared to PBO were 1.932, 3.386, 1.337, and 4.320 (higher values indicate longer

wake bouts) for LEM2.5, LEM5, LEM10, and LEM15, respectively. Unlike other parameters including aSE and SFI, the dose-related improvements were not evident.

Wake-related endpoints

Actigraphy wake efficiency (aWE): The changes from baseline of the mean aWE for the last week on treatment were analyzed using MCP-MOD approach, but no models showed a statistically significant trend. Mean baseline aWE values were 67.19% to 72.53% across all groups. LS mean differences from baseline compared to PBO were –3.437, 1.458, –4.994, and –2.593 percentage points (higher values indicate better wake efficiency) for LEM2.5, LEM5, LEM10, and LEM15, respectively. Increased wake efficiency during the daytime was consistently observed for LEM5 across 4 weeks of treatment.

Wake fragmentation index (WFI): Mean baseline WFI values were 85.72 to 94.76 across all groups. LS mean differences from baseline compared to PBO were 4.845, –3.872, 6.776, and 3.017 (lower values indicate more consolidated wake during the daytime) for LEM2.5, LEM5, LEM10, and LEM15, respectively. More consolidated wake during the daytime was consistently observed for LEM5 across 4 weeks of treatment.

Mean duration of sleep bouts: Mean baseline values were 18.36 to 23.30 across all groups. LS mean differences (95% CI) from baseline compared to PBO were 0.063 (–2.452, 2.579), –0.238 (–2.817, 2.342), –0.293 (–2.745, 2.160), and –1.557 (–4.113, 1.000) (higher values indicate longer sleep bouts) for LEM2.5, LEM5, LEM10, and LEM15, respectively. Duration of sleep bouts (ie, consolidated naps that were 10 min or more in duration) during daytime consistently decreased for LEM5, LEM10, and LEM15 across 4 weeks of treatment.

Circadian rhythm-related endpoints

Interdaily stability (IS): Mean baseline IS values were 0.41 to 0.49 across all groups. LS mean differences from baseline compared to PBO were –0.032, 0.033, –0.052, and 0.005 (higher values indicate stable rhythm) for LEM2.5, LEM5, LEM10, and LEM15, respectively. Increased day-to-day stability of sleep-wake rhythm was consistently observed for LEM5 across 4 weeks of treatment.

Intradaily variability (IV): Mean baseline IV values were 0.90 to 1.10 across all groups. LS mean differences from baseline compared to PBO were 0.086, –0.012, 0.057, and 0.025 (higher values indicate higher fragmentation) for LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating improvement for LEM5.

Least active 5-hour period (L5): Mean baseline L5 values were 1163.2 to 1490.4 activity counts across all groups. LS mean differences (95% CI) from baseline compared to PBO were –389.873 (–739.177, –40.569), –402.994 (–751.670, –54.319), –141.026 (–489.805, 207.752), and –367.845 (–717.870, –17.820) activity counts (higher values indicate restlessness) for LEM2.5, LEM5, LEM10, and LEM15, respectively. More quiescent sleep period during the night were noted with all dose levels of lemborexant. L5 was statistically significantly decreased versus PBO for LEM2.5, LEM5, and LEM15 (P=0.0294, 0.0243, and 0.0398, respectively). Over the 4 weeks of treatment, there was no consistent change in the timing of L5, suggesting no phase shift in the timing of the least active 5 hours of the circadian sleep-wake rhythm, and which always occurred during the nighttime hours.

Most active 10-hour period (M10): Mean baseline M10 values were 8560.4 to 12158.1 activity counts across all groups. LS mean differences from baseline compared to PBO were –1276.180, 227.464, –620.581, and –577.820 activity counts (lower levels indicate inactivity) for LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating improvement for LEM5. Over the 4 weeks of treatment, there were small (less than 1 hour) and inconsistent changes in the start hour of M10 across all groups, suggesting no phase shift in the timing of the most active 10 hours of the circadian sleep-wake rhythm, and which always occurred during the daytime.

Amplitude (AMP): Mean baseline AMP values were 7396.9 to 10994.8 activity counts across all groups. LS mean differences from baseline compared to PBO were –839.088, 651.922, –447.245, and –130.603 activity counts (higher values indicate a more robust circadian rhythm) for LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating improvement for LEM5.

Relative amplitude (RA): Mean baseline RA values were 0.73 to 0.82 across all groups. LS mean differences (95% CI) from baseline compared to PBO were 2.0% (–3.4%, 7.4%), 6.0% (0.5%, 11.5%), 0.3% (–5.1% 5.6%), and 5.7% (0.4%, 11.0%) (higher values indicate rhythms with higher relative amplitude) in LEM2.5, LEM5,

LEM10, and LEM15, respectively. Higher relative amplitudes in circadian sleep-wake rhythms (ie, more distinction between night and day) were noted with all dose levels of lemborexant. RA was statistically significantly increased versus PBO for LEM5 and LEM15 (P=0.0322 and 0.0364, respectively).

Other efficacy endpoints

Total sleep time (TST) during the nighttime: Mean baseline TST values during the night time were 399.13 to 415.49 minutes across all groups. LS mean differences (95% CI) from baseline compared to PBO were –0.586 (–32.916, 31.744), 10.726 (–21.409, 42.860), –1.253 (–32.857, 30.352), and 16.460 (–15.654, 48.574) minutes in LEM2.5, LEM5, LEM10, and LEM15, respectively. Increased TST during the night was consistently observed for LEM5 and LEM15 across 4 weeks of treatment.

Total sleep time (TST) during the daytime: Mean baseline TST values during the daytime were 258.49 to 292.02 minutes across all groups. LS mean differences from baseline compared to PBO were 43.585, –10.341, 48.065, and 25.591 minutes for LEM2.5, LEM5, LEM10, and LEM15, respectively. Decreased TST during the daytime was consistently observed for LEM5 across 4 weeks of treatment.

CGIC-ISWRD: odds ratios for the global score over placebo were 0.50, 1.00, 1.00, and 0.38 for LEM2.5, LEM5, LEM10, and LEM15, respectively, and the dose-related improvements were not evident. Among 4 domain scores, sleep-wake domain generally improved in all treatment groups including PBO.

Rebound sleep and wake fragmentations based on aSE and aWE: When evaluating with aSE, rebounds on sleep efficiency were observed in 66.7%, 23.8%, 23.1%, 52.0%, and 50.0% of subjects for PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating fewer subjects with rebound in all dose levels of lemborexant than PBO. On the other hand, when evaluating with aWE, subjects with rebound on wake efficiency were observed in 37.5%, 47.6%, 42.3%, 58.3%, and 54.2% of subjects, respectively, indicating more rebounders for all dose levels of lemborexant than PBO.

ADAS-cog: LS mean estimates change from baseline were –0.33, –4.81, 0.01, –1.92, and 1.18 in PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating that cognitive function of subjects with ISWRD and AD-D had not worsened in all treatment group; none of these changes were statistically different from PBO. LS mean differences from baseline compared to PBO were –4.48, 0.34, –1.59, and 1.51 (lower scores indicate lower impairment) for LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating statistically significant improvement of cognitive function for LEM2.5 (P=0.0227) but no significant positive or negative effects for other dose levels. [To reviewers: Needs to be verified with new data]

MMSE: LS mean estimates change from baseline were 1.88, 1.96, 1.01, 1.15, and –0.27 in PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating that cognitive function of subjects with ISWRD and AD-D had not worsened in all treatment group. LS mean differences from baseline compared to PBO were 0.08, –0.86, –0.73, and –2.14 (lower scores indicate more impairment) for LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating no apparent positive or negative effects for all dose levels of lemborexant.

Subjects' self-rated EQ-5D-5L VAS scores: LS mean estimates of the change from baseline were 7.38, – 9.33, 6.41, 6.13, and 5.93 (higher scores indicate higher health status) for PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating subjects rated themselves with better overall health at all treatment groups except for LEM2.5. LS mean difference from baseline for LEM2.5 compared to PBO was –16.70, indicating worsening condition.

Caregivers' proxy-rated EQ-5D-5L VAS scores: LS mean estimates of the change from baseline were –5.42, –3.70, –2.62, 2.66, and –0.70 for PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating caregivers rated subjects as in slightly worse overall health in the PBO group. LS mean difference from baseline compared to PBO was 1.72, 2.80, 8.07, and 4.72 for LEM2.5, LEM5, LEM10, and LEM15, indicating improvement for LEM10.

NPI-10 total score: LS mean estimates of the change from baseline were –6.50, –3.77, –2.01, –6.16, and 0.64 (lower scores indicate better neuropsychiatric indices) for PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating improvement of neuropsychiatric indices at all treatment groups except for LEM15, but no superiority to PBO.

SDI score: LS mean estimates of the change from baseline were –0.46, –0.16, –0.30, –0.06, and –0.59 (lower

scores indicate less sleep disturbance) for PBO, LEM2.5, LEM5, LEM10, and LEM15, respectively, indicating improvement of sleep disturbance for all treatment groups, but no superiority to PBO.

Effects on caregivers

Evaluation of effects on caregivers with PSQI (quality and patterns of sleep), ZBI-short form (caregiver's burden), and EQ-5D-5L (Caregiver Self Version) were conducted in the Core Study, but no obvious treatment differences for the caregivers comparing the results from subjects treated with LEM or PBO were observed.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Pharmacokinetics

Lemborexant PK data from Study 202 were compared with other available data from Studies 001, 002, 003, 004, 005, 008, 106, 107, 108, and 201 using population PK models. Limited PK afforded only an assessment of CL/F from this study, which indicated a slightly higher exposure of lemborexant in subjects with ISWRD and AD-D compared to healthy subjects and subjects with primary insomnia. The concentrations of donepezil and memantine appeared similar before and after treatment with lemborexant. No conclusions could be made regarding the impact of lemborexant on galantamine exposure as only 1 subject had observed concentrations.

Pharmacokinetics/Pharmacodynamics

Exposure–response analyses examined the relationship of lemborexant $C_{ave,ss}$ to 7 actigraphy endpoints (aSE, aWE, SFI, mean duration of sleep bouts, mean duration of wake bouts, RA, L5) and TST.

No consistent E-R was apparent across the efficacy endpoints except the average duration of sleep bouts. For this endpoint, a small concentration-dependent percent change from baseline effect (10% to 20%) was noted. The effect is driven largely by exposures associated with the highest dose (LEM15) when the PK/PD analysis used all available data of the study. PK and PK/PD analyses are summarized in a separate, stand-alone report (CPMS-E2006-006R).

Pharmacogenomics

Genotyping of apolipoprotein E was conducted in 53 subjects overall as demographics for subjects; 3 subjects (5.7%) had 2 copies of the E4 allele, and 14 subjects (26.4%) had 1 copy. However, no correlation analyses between the pharmacogenomic data and PK, efficacy or safety data were conducted within this study.

Safety

During the Core Study, 50 subjects (12, 13, 13, and 12 subjects in the LEM2.5, LEM5, LEM10, and LEM15 groups, respectively) were exposed to lemborexant and 12 subjects were exposed to placebo. All subjects received study drug for the entire Treatment Period.

Lemborexant was generally well tolerated in subjects with ISWRD and AD-D. There were no deaths, no treatment-emergent SAEs, and no TEAEs leading to study drug discontinuation reported in the Core Study.

Incidence of TEAEs was slightly higher for the highest dose of LEM15 (50.0%, 6/12 subjects) compared to PBO (33.3%), and similar to PBO in other lemborexant groups (23.1% to 30.8%). The common TEAEs (reported in more than 1 subject in any lemborexant group) were constipation, somnolence, arthralgia, headache, and nightmare, and those events were not reported for PBO, LEM2.5, or LEM5. There were no new safety concerns identified in this study, and the safety profile in this study was consistent with that in subjects with insomnia.

Lemborexant did not worsen the cognitive functions of subjects with ISWRD and AD-D in this study as measured by ADAS-cog and MMSE. There were no trends of clinical concern identified based on analysis of laboratory values, vital signs, body weights, ECGs, or eC-SSRS evaluations.

Morning residual sleepiness: On each of the first 3 and last 3 mornings of the Treatment Period, there were consistent increases in the sum of activity counts compared to baseline for PBO, and consistent decreases in the LEM15 group, suggesting a decrease in activity levels for LEM15 as a result of treatment that may be indicative of next-morning residual sleepiness. There were no other treatment groups in which consistent increases or decreases in the sum of activity counts in the first 3 hours of the morning were observed. The number of sleep bouts during the first 3 hours of the morning was not increased or decreased consistently across either the first

3 mornings or the last 3 mornings of the Treatment Period, suggesting no consistent pattern of increased sleepiness as a result of lemborexant administration on the previous night.

Conclusions

- The changes from baseline of the mean aSE and mean aWE for the last week on treatment were analyzed using MCP-MOD approach, but no models showed a statistically significant trend either for aSE or aWE.
- Increased sleep efficiency as indicated by aSE was consistently observed for LEM2.5 and LEM5 across 4 weeks of treatment. Sleep was more consolidated across the night as indicated by a consistent decrease in SFI in LEM2.5, LEM5, and LEM15 across 4 weeks of treatment. Also, an increase in TST during the night was consistently observed in LEM5 and LEM15 across 4 weeks of treatment.
- Increased wake efficiency was consistently observed for LEM5 across 4 weeks of treatment. Also, duration of sleep bouts (ie, naps that were 10 min or more in duration) during the daytime consistently decreased for LEM5, LEM10, and LEM15 across 4 weeks of treatment.
- Increased day-to-day stability of the sleep-wake rhythm was consistently observed for LEM5 across 4 weeks of treatment.
- Also, more quiescent sleep periods during the night as indicated by L5 and a higher relative amplitude in the sleep-wake rhythm (ie, more distinction between night and day) were observed in all dose levels of lemborexant. The decrease in L5 was statistically significantly larger for LEM2.5, LEM5 and LEM15 compared to PBO, while the increase in relative amplitude was statistically significantly larger for LEM5 and LEM15 compared to PBO.
- Exposure of lemborexant in subjects with ISWRD and AD-D was slightly higher compared to previous studies conducted in healthy subjects and subjects with primary insomnia. Plasma concentrations of donepezil and memantine appear similar before and after treatment with lemborexant.
- No consistent E-R was apparent across the efficacy endpoints except for the average duration of sleep bouts, which was decreased with increasing plasma concentrations.
- Multiple administrations of LEM2.5, LEM5, LEM10, and LEM15 for 28 consecutive nights were well tolerated in subjects with ISWRD and AD-D. There were no deaths, no treatment-emergent SAEs, and no TEAEs leading to study drug discontinuation reported in the Core Study.
- Incidence of TEAEs was slightly higher for the highest dose of LEM15 (50.0%) compared to PBO (33.3%), and similar to PBO in other lemborexant groups (23.1% to 30.8%). No safety concerns arose from laboratory values, vital signs, body weights, ECGs, or eC-SSRS evaluations. There were no new safety concerns found in this study, and the safety profile in the Core Study was consistent with that in subjects with insomnia.
- Lemborexant did not worsen the cognitive functions of subjects with ISWRD and AD-D in this study as measured by ADAS-cog or MMSE. No TEAEs related to cognitive function impairment were reported in the Core Study.
- Among the doses tested, LEM5 results were consistent with improvement in circadian, nighttime, and daytime actigraphy parameters and may be suitable for further clinical assessment.

Date of Report

29 Nov 2018