2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: E2006/lemborexant	Referring to Module 5 of the Dossier	
Name of Active Ingredient: lemborexant	Volume: Page:	

Study Title

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

Investigators/Sites

The Principal Investigator was Russell Rosenberg, PhD, NeuroTrials Research Inc., Atlanta, Georgia. Subjects were randomized into the study at 67 sites (45 sites in the United States, 8 sites in Spain, 6 sites in Germany, 5 sites in Canada, 2 sites in the UK, and 1 site in Italy).

Publication (Reference)

None

Study Period

31 May 2016 to 30 Jan 2018

Phase of Development

Phase 3

Objectives

Primary Objective

To demonstrate using polysomnography (PSG) that lemborexant (lemborexant 10 mg [LEM10] and lemborexant 5 mg [LEM5]) is superior to placebo (PBO) on objective sleep onset as assessed by latency to persisted sleep (LPS) after the last 2 nights of 1 month of treatment in subjects 55 years and older with insomnia disorder.

Secondary Objectives

Key Secondary Objectives – US Only

- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by sleep efficiency (SE) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to PBO on sleep maintenance as assessed by wake after sleep onset (WASO) after the last 2 nights of treatment
- Demonstrate that lemborexant (LEM10 and LEM5) is superior to zolpidem tartrate extended release 6.25 mg (ZOL) on wake after sleep onset in the second half of the night (WASO2H) after the last 2 nights of treatment

Key Secondary Objectives – Non-US Only

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

Additional Secondary Objectives –US and Non-US

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

Exploratory Objectives – US and Non-US

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

Methodology

This was a global, multicenter, randomized, double-blind, placebo-controlled, active comparator (zolpidem), parallel-group study of 2 dose levels of lemborexant for 30 nights in subjects 55 years or older with insomnia disorder. Subjects were males 65 years or older or females 55 years or older. Approximately 60% of the population was to be age 65 years or older.

The study had 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase comprised 3 periods that lasted up to a maximum of 35 days: a Screening Period that included 2 visits; a Run-in Period that began when eligible subjects were dispensed PBO tablets and included 2 consecutive nights

on which PSG was recorded, and a Baseline Period that included the Day 1 assessments. The Randomization Phase was comprised of a Treatment Period during which subjects were treated for 30 nights followed by a minimum 14-day interval before an End of Study (EOS) Visit. The Treatment Period began on Day 1 when subjects were randomized in a double-blinded manner, to receive LEM5, LEM10, ZOL, or PBO. Study drug was administered and overnight PSGs were initiated on the evenings of Day 1 and Day 2. On Day 29 and Day 30, subjects returned to the clinic for overnight PSGs.

Number of Subjects (Planned and Enrolled)

Approximately 950 subjects were planned for enrollment into the study. A total of 1006 subjects were randomized to treatment (LEM5 [266 subjects], LEM10 [269 subjects], ZOL [263 subjects], and PBO [208 subjects]).

Diagnosis and Main Criteria for Inclusion

1. Males age 65 years or older, or females age 55 years or older, at the time of informed consent
2. Met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for Insomnia Disorder, as follows:
   - Complained of dissatisfaction with night time sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint was limited to difficulty initiating sleep, the subject was not eligible)
   - Frequency of complaint 3 or more times per week
   - Duration of complaint greater than or equal to 3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of sWASO typically greater than or equal to 60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reported regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At Screening: Reported habitual bedtime, defined as the time the subject attempted to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. At Screening and at check-in before the first PSG during the Run-in Period: ISI score greater than or equal to 13
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary on the 7 most recent mornings (minimum 5 of 7 for eligibility) before the second screening visit, such that sWASO was greater than or equal to 60 minutes on at least 3 of the 7 nights
8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that neither bedtime (defined as the time the subject attempted to try to sleep), nor waketime (defined as the time the subject got out of bed for the day) deviated more than 1 hour on more than 2 nights from the calculated median habitual sleep time or median habitual waketime, respectively, from the Screening Sleep Diary entries
9. Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary on the 7 most recent mornings before the second screening visit, such that there were not more than 2 nights with time spent in bed duration less than 7 hours or greater than 10 hours
10. During the Run-in Period: Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary on the 7 most recent mornings before the first PSG during the Run-in Period, such that sWASO was greater than or equal to 60 minutes on at least 3 of the 7 nights
11. During the Run-in Period: Reconfirmation of regular bedtimes and waketimes as defined in Inclusion Criterion 8
12. During the Run-in Period: Reconfirmation of sufficient duration of time spent in bed as defined in Inclusion Criterion 9
13. During the Run-in Period: Objective PSG evidence of insomnia as follows: WASO average greater than or equal to 60 minutes on the 2 consecutive PSGs, with neither night less than 45 minutes
14. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours

each night

15. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the subject's participation in the study

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

During the Treatment Period, all subjects received 2 tablets per day according to the treatment group to which the subject had been randomized:

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

Lemborexant 5 mg, lemborexant 10 mg, or lemborexant-matched placebo were taken orally in tablet form each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep. When the subject was to sleep in the clinic for PSG, study personnel administered study drug. On other nights, the subject took the study drug at home on as consistently a time schedule as possible. Batch/lot numbers: 110252, 110254, and 110255.

Comparator Treatments, Dose, Mode of Administration, and Batch Numbers

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

During the Treatment Period, all subjects received 2 tablets per day according to the treatment group to which the subject had been randomized:

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

Zolpidem tartrate extended release 6.25 mg (Ambien CR®) or zolpidem-matched placebo were taken orally in tablet form each night for 30 consecutive nights, immediately before the time the subject intended to try to sleep. When the subject was to sleep in the clinic for PSG, study personnel administered study drug. On other nights, the subject took the study drug at home on as consistently a time schedule as possible. Batch/lot numbers: FH091T and HE114 (zolpidem tartrate); and 91861A0 and 97341D0 (placebo).

Duration of Treatment

Each subject received study drug for approximately 30 days.

Assessments

Demography

Subject demographic information was collected at the Screening Visit. Demographic information included date of birth, sex, and race/ethnicity (where allowed). In applicable countries, to protect personal data, only the year of birth was collected, and the month and date of each subject's date of birth was masked where necessary as 01 January.

Baseline Assessments

Medical History and Physical Examinations

Sleep, medical, and psychiatric history and current medical conditions were recorded at the Screening Visit. All sleep, medical, and psychiatric history within 5 years was noted in the Medical History and Current Medical Conditions electronic case report form. If a subject had a score of 11 to 15 on the Epworth Sleepiness Scale (ESS) at Screening, then the presence of excessive daytime sleepiness was to be recorded in the subject's medical history.

Physical examinations (full or brief) were performed as described in the protocol.

Sleep Disorders History and Screening Battery

The Sleep Disorders Screening Battery was administered only at the Screening Visit, and included the:

- STOPBang Sleep Apnea Questionnaire: a list of 8 questions to be answered Yes or No, which screened potential subjects for obstructive sleep apnea.
- International Restless Legs Scale: a subjective scale comprising 10 questions, which measured severity of

symptoms of restless legs syndrome.

- ESS: a questionnaire that asked subjects to rate their probability of falling asleep, on a scale of increasing probability from 0 to 3 for 8 different situations that most people engage in during their daily lives, which assessed the severity of daytime sleepiness.
- Munich Parasomnia Scale: a scale comprised of 21 questions asking whether the subject had experienced phenomena related to International Classification of Sleep Disorders Version 2 classified parasomnias (eg, enuresis, sleepwalking, sleep paralysis) along with a time frame for occurrences of these experiences ranging from within the past month to lifetime and frequency within the time frame ranging from occasionally to almost every night. An adapted version was used.

Beck Depression Inventory – II

The Beck Depression Inventory – II (BDI-II) is a 21-question multiple-choice self-report questionnaire that subjects used to rate the presence, frequency, and severity of symptoms of depression using a 4 point Likert scale. Scores on the BDI-II could have ranged from 0 to 63, with higher scores indicating higher levels of depressive symptoms. Subjects with BDI-II scores greater than 19 were excluded from participation.

Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) is a 21-question multiple-choice self-report inventory that subjects used to rate the presence, frequency, and severity of symptoms of anxiety using a 4-point Likert scale. Scores on the BAI could have ranged from 0 to 63, with higher scores indicating higher levels of anxiety symptoms. Subjects with scores on the BAI greater than 15 were excluded from participation.

Efficacy Assessments

Polysomnography

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

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

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

The following parameters were derived from all PSGs:

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

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

- Sleep onset latency: minutes from lights off to the first epoch of any stage of sleep (N1, N2, N3, rapid eye movement [REM])

- Number of awakenings after persistent sleep, with an awakening defined as at least 2 consecutive epochs of wakefulness; an awakening could not be interrupted by stage N1, but must have been interrupted by stage N2, N3, or REM
- Number of long awakenings
- Wake after sleep onset in the first half of the night (WASO1H): minutes of wake during the interval from onset of persistent sleep until 240 minutes after lights off
- Percentage of stage wake and sleep stages per TIB: wake, non-REM (NREM) sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TIB: wake, NREM sleep (stages N1, N2, N3), REM sleep
- Percentage of sleep stages per TST: NREM sleep (stages N1, N2, N3 separately and combined), REM sleep
- Minutes of sleep stages per TST: NREM sleep (stages N1, N2, N3), REM sleep
- REM episode frequency and duration
- Mean REM/NREM cycle duration
- REM latency: minutes from first epoch of sleep (N1, N2, or N3) to first epoch of REM

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

Electronic Sleep Diary

The Sleep Diary was completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-up Period. Sleep Diary entries could have been maintained in paper format as a backup to the electronic Sleep Diary, if necessary. This diary yielded several self-reported measures of sleep that were used to determine eligibility, as well as to assess efficacy and safety.

Subjects must have complied with requirements for completion of the Sleep Diary. Failure to comply required discussion with the medical monitor and could have resulted in discontinuation of the subject from the study.

Sleep Parameters

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

Quality of Sleep

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

Morning Sleepiness

The Sleep Diary was also used to assess subjective ratings of morning sleepiness with the following question: "How alert/sleepy do you feel this morning?" Subjects rated their sleepiness or alertness level on a scale from

1 to 9, with 1 being extremely sleepy and 9 being extremely alert.

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

Alcohol Consumption

The Sleep Diary included questions that asked whether or not the subject consumed alcohol the previous day within 3 hours before bedtime or exceeded the daily maximum of 2 alcoholic drinks.

Insomnia Severity Index

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

Fatigue Severity Scale

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

Pharmacokinetic Assessments

A single blood sample of 4 mL to determine plasma concentrations of lemborexant and its metabolites (M4, M9, and M10) or zolpidem was obtained within 2 hours predose on Day 2 and Day 30, and within 1 hour after morning waketime on Day 3 and Day 31. The sample handling and shipment of blood samples were described in the central laboratory manual provided to the sites. Plasma concentrations of lemborexant and its metabolites were determined using a validated liquid chromatography-tandem mass spectrometry assay method. Plasma concentrations of zolpidem were not determined, as there were no required instances (serious adverse event/adverse event [SAE/AE]) as directed by the study director or medical monitor. The time and date of the 2 most recent doses preceding the samples obtained on Day 2 and Day 30 were documented.

Pharmacodynamic Assessments

Postural Stability using the Cognitive Drug Research Posture Assessment

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

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

Cognitive Performance Assessment Battery

A computerized performance assessment battery (PAB) was administered on a laptop computer after the postural stability test. While completing the PAB, subjects were in bed and ambient lighting was maintained at a level of 80 to 100 lux at the subject's eye level. On the evening of the Screening PSG visit, before bedtime, subjects were introduced to the PAB tasks and underwent a minimum of 2 training sessions. If subjects could not

adequately perform the tasks during the training sessions, they were excluded from further participation. On the morning after the Screening PSG, subjects completed a session of the cognitive PAB for familiarization purposes only; no data from this session were used for analyses. This session must have been conducted under the same conditions (eg, lighting, subject in bed) as during the testing sessions at subsequent visits.

The PAB comprised 9 tasks, including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Word Recognition, Picture Recognition, Numeric Working Memory, and Spatial Working Memory. The full PAB took approximately 18 to 30 minutes to complete. Four composite domain factor scores were calculated by combining outcome variables from the various tests.

Pharmacogenomic Assessments

Not applicable.

Safety Assessments

Safety assessments consisted of monitoring and recording all AEs; regular laboratory evaluation for hematology, chemistry, and urinalysis; periodic measurement of vital signs, weight and ECGs; and the performance of physical evaluations. Safety was assessed at every clinical visit throughout the study, and at the EOS Visit.

Columbia-Suicide Severity Rating Scale

Suicidality was assessed using a self-rated electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). The eC-SSRS assessed an individual's degree of suicidality, including both suicidal ideation and suicidal behavior.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire

An assessment of withdrawal symptoms was made using Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) completed at the EOS Visit. Subjects were asked about the presence or absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject was to respond "No" (Score=0), "Yes – moderate" (Score=1) or "Yes – Severe" (Score=2). The sum of responses was the subject's score.

Other

EQ-5D-3L

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

Patient Global Impression – Insomnia

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

Statistical Methods

Details of statistical methods and analyses were specified in the statistical analysis plan (SAP Version 3.0, 05 Feb 2018).

Endpoints

Unless specified otherwise, all efficacy and PD endpoints were derived by calculating the averages of pairs of values (eg, average of LPS on Day 1 and Day 2 [denoted as Days 1/2 thereafter], average of LPS on Day 29 and Day 30 [denoted as Days 29/30 thereafter], etc).

Primary Endpoint

The primary endpoint was the change from baseline for mean LPS on Days 29 and 30 of LEM10 and LEM5 compared to PBO.

Secondary Endpoints

Key Secondary Endpoints – US Only

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

Key Secondary Endpoints – Non-US Only

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

Additional Secondary Endpoints – US and Non-US

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

Exploratory Endpoints

The change from baseline for WASO2H for LEM10 and LEM5 compared to ZOL was considered exploratory

for non-US. The following endpoints were also explored for LEM5 and LEM10. Except for PK endpoints, comparisons to both ZOL and PBO were made.

- Change from baseline for the mean rating on the Quality of Sleep question from the Sleep Diary for the first 7 days and last 7 days of the Treatment Period
- Change from baseline for mean power of attention, mean quality of memory, mean continuity of attention, and mean speed of memory retrieval on Days 30 and 31
- From the postural stability test, change from baseline for mean units of body sway after the first 2 nights of the Treatment Period compared to PBO and the last 2 nights of the Treatment Period compared to ZOL and PBO
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-up Period
  - Change from baseline for sSOL on each of the first 3 nights, mean sSOL of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-up Period
  - Change from baseline for sWASO on each of the first 3 nights, mean sWASO of the first 3 nights, mean sWASO of the first 7 and mean sWASO of the second 7 nights of the Follow-up Period
  - Proportion of subjects whose sSOL was longer than at Screening at the following time points during the Follow-up Period by at least 5 minutes: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
  - Proportion of subjects whose sWASO was higher than at Screening at the following time points during the Follow-up Period by at least 5 minutes: each of the first 3 nights, mean of the first 3 nights, mean of the first 7 nights, mean of the second 7 nights
- Mean rating on the morning sleepiness item of the Sleep Diary over the first 7 mornings and last 7 mornings of the Treatment Period
- Mean rating on the morning sleepiness item of the Sleep Diary over the first 7 mornings and last 7 mornings of the Follow-up Period
- Change from baseline for mean morning sleepiness ratings assessed at 1.5 hours after wake time when subjects are in the clinic on Days 1 and 2, and Days 29 and 30
- Change from baseline for mean minutes and mean percentage (a) per TIB and (b) per TST of sleep stage N1, N2, N3 (separately and combined) and REM on Days 1 and 2 and Days 29 and 30
- Change from baseline for mean REM latency
- Change from baseline for mean number of awakenings, and mean number of long awakenings at Days 1 and 2 and Days 29 and 30
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item at Day 31
- Change from baseline on the EQ-5D-3L at Day 31
- Mean score on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at EOS
- Proportion of subjects who scored greater than or equal to 3 on the T-BWSQ of LEM5 and LEM10 compared to ZOL and PBO at EOS
- PK of lemborexant and its metabolites M4, M9, and M10
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

Other Endpoints

The following PSG endpoints were explored on an exploratory basis:

- WASO1H
- Duration of awakenings after persistent sleep
- Duration of long awakenings after persistent sleep
- Minutes and percentage of sleep stages per TIB: wake, NREM (N1, N2, N3 separately and combined), REM
- Minutes and percentage of sleep stages per TST: NREM (N1, N2, N3 separately and combined), REM
- WASO by quarter of the night

Definition of Analysis Sets

Safety Analysis Set: 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.

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

PK Analysis Set: the PK analysis set was the group of subjects who had at least 1 quantifiable plasma concentration of lemborexant or its metabolites, or zolpidem, with adequately documented dosing history.

Per Protocol (PP) Analysis Set: The PP Analysis Set was the group of all randomized subjects who received protocol-assigned study drug and did not have a major protocol deviation that was likely to affect the primary or key secondary efficacy endpoints. These included:

- Randomized during the Run-in Period prior to Randomization visit 5
- Deviations of treatment assignment, treatment administration, and/or dispensing:
  - Subject received the wrong dose
  - Subject completed PSG assessment on Visits 7 and 8 without being dosed

Efficacy Analyses

Unless specified otherwise, all efficacy endpoints were summarized and analyzed using the FAS.

Primary Efficacy Analysis

The primary efficacy endpoint was the change from baseline for LPS on Days 29/30 of LEM10 and LEM5 compared to PBO.

The null hypothesis of the primary objective was that no difference existed in the mean change from baseline for LPS of Days 29/30 for treatment with LEM10 (or LEM5) as compared to PBO, and the corresponding alternative hypothesis was that a difference existed in the mean change from baseline for LPS of Days 29/30 for LEM10 (or LEM5) compared to PBO.

The change from baseline for LPS on Days 1/2 and Days 29/30 was analyzed using the mixed effect model repeated measurement (MMRM) analysis with factors of age group (55 to <65 years and ≥65 years), geographic region (North America and Europe), treatment, visit (Days 1/2 and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline LPS as a covariate based on the FAS. Since LPS is known to be non-normally distributed, a log-transformation was used in the analysis. The unstructured covariance matrix (UN) was used in the analysis. In the case of nonconvergence of UN, the autoregressive [AR(1)] covariance matrix was used in the model. Before the implementation of the MMRM model, the missing values were imputed using a pattern-mixture model utilizing multiple imputation (MI) assuming the missing values were missing not at random (MNAR) utilizing the complete case missing value pattern (subjects who completed all primary efficacy assessments without missing values). The missing values for a given visit were imputed using all available values including the retrieved measurement from the postdiscontinuation data.

The treatment comparison was performed using contrasts. The *P* value, least squares (LS) means, and the 95%

CI for the treatment difference were also provided.

The MI steps for the primary endpoint are detailed in the SAP.

Secondary Efficacy Analyses

Key Secondary Efficacy Analyses

The key secondary analyses of the study were:

- Change from baseline for SE on Days 29/30
- Change from baseline for WASO2H on Days 29/30
- Change from baseline for WASO on Days 29/30

For all key secondary analyses, the change from baseline on Days 1/2 and on Days 29/30 was analyzed using the same MMRM model as the primary efficacy endpoint with factors of age group (55 to <65 years and ≥65 years), geographic region (North America and Europe), treatment, visit (Days 1/2 and Days 29/30), and treatment-by-visit interaction as fixed effect, and baseline as covariates based on the FAS. The UN was used in the analysis. In case of nonconvergence, the AR(1) was used in the model. The missing values were imputed using a pattern mixture model utilizing MI assuming MNAR. Before the implementation of the MMRM model, the missing values for a given visit were imputed using all available values including the retrieved measurement from the postdiscontinuation data.

Other Secondary Efficacy Analyses

Unless it was covered by the same model as the primary and secondary efficacy endpoints, or specified otherwise, for all other secondary endpoints, the change from baseline assessments were analyzed using MMRM assuming missing at random (MAR) (no missing value imputation) and the portion of responders was analyzed using the Cochran–Mantel–Haenszel (CMH) test adjusted for age group.

Exploratory Efficacy/Pharmacodynamic Analyses

Unless specified otherwise, for all exploratory efficacy analyses endpoints, the change from baseline assessment was analyzed using MMRM assuming MAR and the portion of responders was analyzed using the CMH test adjusted for age group. Missing values were considered as non-responders in all responder analyses. No multiplicity adjustment was made for any of the exploratory analyses.

Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The plasma concentrations of lemborexant and its metabolites M4, M9, and M10 were summarized using descriptive statistics by dose, time, and day based on the Safety Analysis Set. Plasma concentrations of zolpidem were not summarized or listed as there was no subject in whom zolpidem concentrations were required to be measured.

Pharmacokinetic/Pharmacodynamic Analyses

A separate analysis plan for the PK/PD analyses was developed and finalized before the database lock.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

All safety analyses were performed based on observed data using the Safety Analysis Set. Safety data were summarized on an "as treated" basis using descriptive statistics or frequency count only. No hypothesis testing was performed for safety analyses.

Other Analyses

EQ-5D-3L

The EQ-5D-3L instrument comprised questions on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (EQ VAS). Each dimension score was summarized separately at Baseline and Day 31 using frequency count on observed data only with no imputation. The change from baseline for EQ VAS was analyzed using analysis of covariance with factors of age group (55 to <65 years and ≥65 years old), geographic region (North America and Europe), and treatment based on the

FAS.

Patient Global Impression – Insomnia

Each item on the PGI-Insomnia questionnaire was analyzed and summarized separately ("positive medication effect" vs others for the first 3 items; "just right" vs others for the last item) using chi-square test on observed data only based on the FAS with no imputation for missing values, and repeated for age subgroups.

Determination of Sample Size

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

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

Power was also estimated for the key secondary objective, the comparison of LEM10 and LEM5 to PBO on change from baseline for SE and WASO, and LEM10 and LEM5 to ZOL on WASO2H. A sample size of 250 subjects each for LEM5, LEM10, and ZOL, and 200 subjects for PBO had at least a 95% power for detecting a statistically significant difference between lemborexant and PBO for change from baseline for SE, at least 80% power for detecting a statistically significant difference between LEM10 and ZOL/PBO for change from baseline for WASO2H/WASO based on a 2-sided 2-sample t-test at the 5% significance level.

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

Estimated treatment difference and SD were based on Study 201.
LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LPS = latency to persistent sleep, min = minutes, PBO = placebo, SE = sleep efficiency, WASO = wake after sleep onset, WASO2H = wake after sleep onset in the second half of the night, ZOL = zolpidem tartrate extended release 6.25 mg.

Results

Subject Disposition/Analysis Sets

A total of 3537 subjects signed informed consent for entry into the study. A total of 535 subjects were randomized to the lemborexant treatment groups (269 subjects in LEM10 and 266 subjects in LEM5), while 263 and 208 subjects were randomized to the ZOL and PBO treatment groups, respectively. All randomized subjects were treated with study drug. The majority of subjects in all treatment groups completed the study (96.7%, 97.0%, 93.5%, and 95.2% of subjects in the LEM10, LEM5, ZOL, and PBO treatment groups, respectively). All subjects were included in the FAS and Safety Analysis Set; however, 1 subject randomized to the LEM10 treatment group actually received placebo so is included in the PBO treatment group for the Safety Analysis Set.

Efficacy

Primary Efficacy Endpoint (LPS)

Median LPS for PBO was 33.6 minutes at Baseline and decreased to 25.8 minutes at Days 29/30, resulting in a median change from baseline of –6.6 minutes.

Median LPS for LEM10 was 38.5 minutes at Baseline and decreased to 19.3 minutes at Days 29/30, resulting in a median change from baseline of –16.3 minutes. Median LPS for LEM5 was 33.1 minutes at Baseline and decreased to 18.8 minutes at Days 29/30, resulting in a median change from baseline of –12.0 minutes. These decreases were larger and statistically significantly different for LEM10 compared to PBO (least squares geometric mean [LSGM] treatment ratio 0.723; $P<0.0001$) and for LEM5 compared to PBO (LSGM treatment ratio 0.773; $P=0.0003$).

Key Secondary Efficacy Endpoints

Sleep Efficiency

Mean SE for PBO was 68.9% at Baseline and increased to 74.5% at Days 29/30, resulting in a mean change from baseline of 5.4%.

Mean SE for LEM10 was 67.9% at Baseline and increased to 82.0% at Days 29/30, resulting in a mean change from baseline of 14.1%. Mean SE for LEM5 was 68.4% at Baseline and increased to 81.3% at Days 29/30, resulting in a mean change from baseline of 12.9%. These increases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 8.0%; $P<0.0001$) and for LEM5 compared to PBO (LS mean treatment difference 7.1%; $P<0.0001$).

WASO

Mean WASO for PBO was 111.8 minutes at Baseline and decreased to 92.1 minutes at Days 29/30, resulting in a mean change from baseline of –18.6 minutes.

Mean WASO for LEM10 was 114.8 minutes at Baseline and decreased to 68.6 minutes at Days 29/30, resulting in a mean change from baseline of –46.4 minutes. Mean WASO for LEM5 was 113.4 minutes at Baseline and decreased to 69.1 minutes at Days 29/30, resulting in a mean change from baseline of –43.9 minutes. These decreases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –25.4 minutes; $P<0.0001$) and for LEM5 compared to PBO (LS mean treatment difference –24.0 minutes; $P<0.0001$).

WASO2H

Mean WASO2H for ZOL was 78.0 minutes at Baseline and decreased to 56.7 minutes at Days 29/30, resulting in a mean change from baseline of –21.4 minutes.

Mean WASO2H for LEM10 was 76.9 minutes at Baseline and decreased to 48.2 minutes at Days 29/30, resulting in a mean change from baseline of –28.8 minutes. Mean WASO2H for LEM5 was 76.6 minutes at Baseline and decreased to 49.1 minutes at Days 29/30, resulting in a mean change from baseline of –27.2 minutes. These decreases were larger and statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference –8.0 minutes; $P=0.0005$) and for LEM5 compared to ZOL (LS mean treatment difference –6.7 minutes; $P=0.0038$).

Other Secondary Efficacy Endpoints

Polysomnography Endpoints Versus Placebo at Days 1/2 and Days 29/30

LPS

Median LPS for PBO was 33.6 minutes at Baseline and decreased to 27.3 minutes at Days 1/2, resulting in a median change from baseline of –6.3 minutes.

Median LPS for LEM10 was 38.5 minutes at Baseline and decreased to 21.8 minutes at Days 1/2, resulting in a median change from baseline of –10.5 minutes. Median LPS for LEM5 was 33.1 minutes at Baseline and decreased to 21.6 minutes at Days 1/2, resulting in a median change from baseline of –10.0 minutes. These decreases were larger and statistically significantly different for LEM10 compared to PBO (LSGM treatment ratio 0.795; *P*=0.0002) and for LEM5 compared to PBO (LSGM treatment ratio 0.850; *P*=0.0092).

Sleep Efficiency

Mean SE for PBO was 68.9% at Baseline and increased to 73.1% at Days 1/2, resulting in a mean change from baseline of 4.2%.

Mean SE for LEM10 was 67.9% at Baseline and increased to 84.3% at Days 1/2, resulting in a mean change from baseline of 16.5%. Mean SE for LEM5 was 68.4% at Baseline and increased to 82.0% at Days 1/2, resulting in a mean change from baseline of 13.6%. These increases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 11.6%; *P*<0.0001) for LEM5 compared to PBO (LS mean treatment difference 9.0%; *P*<0.0001).

WASO

Mean WASO for PBO was 111.8 minutes at Baseline and decreased to 96.7 minutes at Days 1/2, resulting in a mean change from baseline of –15.1 minutes.

Mean WASO for LEM10 was 114.8 minutes at Baseline and decreased to 55.2 minutes at Days 1/2, resulting in a mean change from baseline of –59.6 minutes. Mean WASO for LEM5 was 113.4 minutes at Baseline and decreased to 63.5 minutes at Days 1/2, resulting in a mean change from baseline of –50.0 minutes. These decreases from baseline were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –42.3 minutes; *P*<0.0001) and for LEM5 compared to PBO (LS mean treatment difference –33.4 minutes; *P*<0.0001).

WASO2H

Mean WASO2H for PBO was 74.4 minutes at Baseline and decreased to 67.4 and 64.4 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of –7.1 and –8.9 minutes, respectively.

Mean WASO2H for LEM10 was 76.9 minutes at Baseline and decreased to 39.8 and 48.2 minutes at Days 1/2 and Days 29/30, respectively, resulting in mean changes from baseline of –37.1 and –28.8 minutes, respectively. Mean WASO2H for LEM5 was 76.6 minutes at Baseline and decreased to 46.3 and 49.1 minutes at Days 1/2 and Days 29/30, respectively, resulting in mean changes from baseline of –30.3 and –27.2 minutes, respectively. These decreases were larger and statistically significantly different for LEM10 compared to PBO at Days 1/2 (LS mean treatment difference –28.3 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference –17.8 minutes; *P*<0.0001) and for LEM5 compared to PBO at Days 1/2 (LS mean treatment difference –21.7 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference –16.4 minutes; *P*<0.0001).

TST

Mean TST for PBO was 330.7 minutes at Baseline and increased to 350.1 and 357.5 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of 19.4 and 25.7 minutes, respectively.

Mean TST for LEM10 was 325.1 minutes at Baseline and increased to 404.7 and 393.2 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of 79.6 and 67.9 minutes, respectively. Mean TST for LEM5 was 328.0 minutes at Baseline and increased to 393.2 and 390.0 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of 65.2 and 62.0 minutes, respectively. These increases were larger and statistically significantly different for LEM10 compared to PBO at Days 1/2 (LS mean treatment difference 56.9 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference 38.9 minutes; *P*<0.0001) and for LEM5 compared to PBO at Days 1/2 (LS mean treatment difference 44.1 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference 34.2 minutes; *P*<0.0001).

Polysomnography Endpoints Versus Zolpidem at Days 1/2 and Days 29/30

LPS

Median LPS for ZOL was 31.5 minutes at Baseline and decreased to 27.0 and 28.5 minutes at Days 1/2 and Days 29/30, respectively, resulting in a median change from baseline of –5.6 and –2.9 minutes, respectively.

The treatment differences for change from baseline in LPS were larger and statistically significantly different for LEM10 compared to ZOL at Days 1/2 (LSGM treatment ratio 0.818; *P*=0.0006) and Days 29/30 (LSGM treatment ratio 0.594; *P*<0.0001) and for LEM5 compared to ZOL at Days 1/2 (LSGM treatment ratio 0.874; *P*=0.0218) and Days 29/30 (LSGM treatment ratio 0.634; *P*<0.0001).

Sleep Efficiency

Mean SE for ZOL was 68.1% at Baseline and increased to 79.9% and 77.2% at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of 11.7% and 9.1%, respectively.

The treatment differences for change from baseline in SE were larger and statistically significantly different for LEM10 compared to ZOL at Days 1/2 (LS mean treatment difference 4.6%; *P*<0.0001) and Days 29/30 (LS mean treatment difference 4.9%; *P*<0.0001) and for LEM5 compared to ZOL at Days 1/2 (LS mean treatment difference 2.1%; *P*=0.0011) and Days 29/30 (LS mean treatment difference 3.9%; *P*<0.0001).

WASO

Mean WASO for ZOL was 114.3 minutes at Baseline and decreased to 69.9 and 77.7 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of –44.4 and –36.5 minutes, respectively.

The treatment differences for change from baseline in WASO were larger and statistically significantly different for LEM10 compared to ZOL at Days 1/2 (LS mean treatment difference –15.0 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference –9.1 minutes; *P*=0.0016) and for LEM5 compared to ZOL at Days 1/2 (LS mean treatment difference –6.2 minutes; *P*=0.0154)) and Days 29/30 (LS mean treatment difference –7.7 minutes; *P*=0.0073).

WASO2H

Mean WASO2H for ZOL was 78.0 minutes at Baseline and decreased to 53.3 minutes at Days 1/2, resulting in a mean change from baseline of –24.6 minutes.

The treatment differences for change from baseline in WASO2H were larger and statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference –13.1 minutes; *P*<0.0001) and for LEM5 compared to ZOL (LS mean treatment difference –6.5 minutes; *P*=0.0020) at Days 1/2.

TST

Mean TST for ZOL was 327.0 minutes at Baseline and increased to 382.4 and 370.3 minutes at Days 1/2 and Days 29/30, respectively, resulting in a mean change from baseline of 55.3 and 43.3 minutes, respectively.

The treatment differences for change from baseline in TST were larger and statistically significantly different for LEM10 compared to ZOL at Days 1/2 (LS mean treatment difference 23.1 minutes; *P*<0.0001) and Days 29/30 (LS mean treatment difference 24.1 minutes; *P*<0.0001) and for LEM5 compared to ZOL at Days 1/2 (LS mean treatment difference 10.3 minutes; *P*=0.0010) and Days 29/30 (LS mean treatment difference 19.4 minutes; *P*<0.0001).

Electronic Sleep Diary Endpoints Versus Placebo

sSOL

Median sSOL for PBO was 49.3 minutes at Baseline and decreased to 41.7 and 38.6 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a median change from baseline of –2.9 and –4.0 minutes, respectively.

Median sSOL for LEM10 was 53.6 minutes at Baseline and decreased to 29.6 and 27.5 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a median change from baseline of –15.0 and –17.1 minutes, respectively. Median sSOL for LEM5 was 58.6 minutes at Baseline and decreased to 34.3 minutes and 30.4 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a median change from baseline of –14.9 and –18.5 minutes, respectively. These decreases were larger and comparison with PBO indicated a statistically significantly different for LEM10 compared to PBO over the first 7 nights (LSGM treatment ratio 0.753; *P*<0.0001) and last 7 nights (LSGM treatment ratio 0.689; *P*<0.0001) of the Treatment Period and for LEM5 compared to PBO over the first 7 nights (LSGM treatment ratio 0.815; *P*<0.0001) and last 7 nights (LSGM treatment ratio 0.750; *P*<0.0001) of the Treatment Period.

sSE

Mean sSE for PBO was 56.1% at Baseline and increased to 62.5% and 64.0% over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 6.7% and 8.4%,

respectively.

Mean sSE for LEM10 was 54.3% at Baseline and increased to 68.1% and 69.9% over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 14.0% and 16.1%, respectively. Mean sSE for LEM5 was 56.1% at Baseline and increased to 66.0% and 68.2% over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 10.6% and 12.9%, respectively.

These increases were larger and statistically significantly different for LEM10 compared to PBO over the first 7 nights (LS mean treatment difference 6.8%; $P<0.0001$) and last 7 nights (LS mean treatment difference 7.2%; $P<0.0001$) of the Treatment Period and for LEM5 compared to PBO over the first 7 nights (LS mean treatment difference 3.8%; $P=0.0008$) and last 7 nights (LS mean treatment difference 4.6%; $P=0.0005$) of the Treatment Period.

sWASO

Mean sWASO for PBO was 170.9 minutes at Baseline and decreased to 143.5 and 135.9 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of –27.9 and –36.0 minutes, respectively.

Mean sWASO for LEM10 was 175.4 minutes at Baseline and decreased to 119.8 and 117.1 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of –55.1 and –58.0 minutes, respectively. Mean sWASO for LEM5 was 166.8 minutes at Baseline and decreased to 127.4 and 119.3 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of –39.3 and –44.5 minutes, respectively. These decreases were larger and statistically significantly different for LEM10 compared to PBO over the first 7 nights (LS mean treatment difference –26.3 minutes; $P<0.0001$) and last 7 nights (LS mean treatment difference –20.6 minutes; $P=0.0002$) of the Treatment Period and for LEM5 compared to PBO over the first 7 nights (LS mean treatment difference –12.4 minutes; $P=0.0093$) and last 7 nights (LS mean treatment difference –11.5 minutes; $P=0.0396$) of the Treatment Period.

sTST

Mean sTST for PBO was 276.2 minutes at Baseline and increased to 305.4 and 312.5 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 30.9 and 39.0 minutes, respectively.

Mean sTST for LEM10 was 266.1 minutes at Baseline and increased to 332.9 and 343.7 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 67.8 and 80.0 minutes, respectively. Mean sTST for LEM5 was 275.7 minutes at Baseline and increased to 322.7 and 334.2 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 50.3 and 62.4 minutes, respectively. These increases were larger and statistically significantly different for LEM10 compared to PBO over the first 7 nights (LS mean treatment difference 34.5 minutes; $P<0.0001$) and last 7 nights (LS mean treatment difference 37.8 minutes; $P<0.0001$) of the Treatment Period and for LEM5 compared to PBO over the first 7 nights (LS mean treatment difference 19.1 minutes; $P=0.0007$) and last 7 nights (LS mean treatment difference 23.6 minutes; $P=0.0003$) of the Treatment Period.

Electronic Sleep Diary Endpoints Versus Zolpidem

sSOL

Median sSOL for ZOL was 53.2 minutes at Baseline and decreased to 38.1 and 37.5 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a median change from baseline of –10.0 and –10.7 minutes, respectively.

The treatment differences for change from baseline in sSOL were larger and statistically significantly different for LEM10 compared to ZOL over the first 7 nights (LSGM treatment ratio 0.830; $P<0.0001$) and last 7 nights (LSGM treatment ratio 0.811; $P<0.0001$) of the Treatment Period and for LEM5 over the first 7 nights (LSGM treatment ratio 0.898; $P=0.0122$) and last 7 nights (LSGM treatment ratio 0.882; $P=0.0176$) of the Treatment Period.

sSE

Mean sSE for ZOL was 55.5% at Baseline and increased to 66.5% and 69.5% over the first 7 nights and last

7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 12.0% and 14.8%, respectively.

The treatment differences for change from baseline in sSE were larger but not statistically different for LEM10 compared to ZOL over the first 7 nights (LS mean treatment difference 1.7%; *P*=0.1093) and last 7 nights (LS mean treatment difference 1.1%; *P*=0.4013) of the Treatment Period.

The treatment differences for change from baseline in sSE were smaller and not statistically significant for LEM5 compared to ZOL over the first 7 nights (LS mean treatment difference –1.4%; *P*=0.1963) and last 7 nights (LS mean treatment difference –1.5%; *P*=0.2196) of the Treatment Period.

sWASO

Mean sWASO for ZOL was 173.1 minutes at Baseline and decreased to 124.8 and 109.6 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of –48.9 and –63.5 minutes, respectively.

The treatment differences for change from baseline in sWASO were larger and not statistically significant for LEM10 compared to ZOL over the first 7 nights of the Treatment Period (LS mean treatment difference –5.8 minutes; *P*=0.1949), and smaller and not statistically significant for LEM10 compared to ZOL over the last 7 nights of the Treatment Period (LS mean treatment difference 5.4 minutes; *P*=0.3064).

The treatment differences for change from baseline in sWASO were smaller and not statistically significant for LEM5 compared to ZOL over the first 7 nights of the Treatment Period (LS mean treatment difference 8.1 minutes; *P*=0.0706), and smaller and statistically significant for LEM5 compared to ZOL over the last 7 nights of the Treatment Period (LS mean treatment difference 14.5 minutes; *P*=0.0059).

sTST

Mean sTST for ZOL was 273.1 minutes at Baseline and increased to 325.6 and 340.2 minutes over the first 7 nights and last 7 nights of the Treatment Period, respectively, resulting in a mean change from baseline of 57.0 and 71.0 minutes, respectively.

The treatment differences for change from baseline in sTST were larger but not statistically significant for LEM10 compared to ZOL over the first 7 nights (LS mean treatment difference 8.9 minutes; *P*=0.0949) and last 7 nights (LS mean treatment difference 7.4 minutes; *P*=0.2317) of the Treatment Period.

The treatment differences for change from baseline in sTST were smaller and not statistically significant for LEM5 compared to ZOL over the first 7 nights (LS mean treatment difference –6.6 minutes; *P*=0.2174) and last 7 nights (LS mean treatment difference –6.8 minutes; *P*=0.2718) of the Treatment Period.

Responder Analysis

Objective Sleep Onset Responders

As a result of the inclusion criteria where subjects were not required to have sleep onset complaints, the number of subjects eligible for this analysis was n=155, n=147, n=118, and n=140 for LEM10, LEM5, PBO, and ZOL, respectively.

The differences in the proportion of objective sleep onset responders for LEM10 compared to PBO and for LEM5 compared to PBO at Days 1/2 and Days 29/30 were not statistically significant.

The differences in the proportion of objective sleep onset responders were larger and statistically significant for LEM10 compared to ZOL at Days 1/2 (11.7%; *P*=0.0218) and Days 29/30 (17.3%; *P*=0.0013), and for LEM5 compared to ZOL at Days 29/30 (15.5%; *P*=0.0040). The difference in the proportion of objective sleep onset responders for LEM5 compared ZOL at Days 1/2 was not statistically significant.

Subjective Sleep Onset Responders

The number of subjects eligible for this analysis was n=194, n=211, n=150, and n=203 for LEM10, LEM5, PBO, and ZOL, respectively.

The differences in the proportion of subjective sleep onset responders were larger and statistically significant for LEM10 compared to PBO and for LEM5 compared to PBO over the first 7 nights (10.0%; *P*=0.0021 and 8.1%; *P*=0.0076, respectively) and last 7 nights (10.2%; *P*=0.0101 and 11.6%; *P*=0.0036, respectively) of the Treatment Period.

The differences in the proportion of subjective sleep onset responders for LEM10 compared to ZOL and for LEM5 compared to ZOL over the first 7 nights of the Treatment Period were not statistically significant.

The differences in the proportion of subjective sleep onset responders were larger and statistically significant for LEM10 compared to ZOL (8.8%; *P*=0.0165) and for LEM5 compared to ZOL (10.0%; *P*=0.0063) over the last 7 nights of the Treatment Period.

Objective Sleep Maintenance Responders

Since the inclusion criteria required that subjects meet criteria for sleep maintenance complaints, the number of subjects eligible for this analysis was higher with n=266, n=266, n=205, and n=261 for LEM10, LEM5, PBO, and ZOL, respectively.

The differences in the proportion of objective sleep maintenance responders were larger and statistically significant for LEM10 compared to PBO and for LEM5 compared to PBO at Days 1/2 (48.2%; *P*<0.0001 and 34.1%; *P*<0.0001, respectively) and Days 29/30 (24.5%; *P*<0.0001 and 21.9%; *P*<0.0001, respectively).

The differences in the proportion of objective sleep maintenance responders were larger and statistically significant for LEM10 compared to ZOL at Days 1/2 (18.7%; *P*<0.0001) and Days 29/30 (11.7%; *P*=0.0048), and for LEM5 compared to ZOL at Days 29/30 (9.3%; *P*=0.0283). The difference in the proportion of objective sleep maintenance responders for LEM5 compared to ZOL at Days 1/2 was not statistically significant.

Subjective Sleep Maintenance Responders

The number of subjects eligible for this analysis was n=260, n=255, n=197, and n=251 for LEM10, LEM5, PBO, and ZOL, respectively.

The differences in the proportion of subjective sleep maintenance responders were larger and statistically significant for LEM10 compared to PBO and for LEM5 compared to PBO over the first 7 nights (11.0%; *P*=0.0017 and 7.5%; *P*=0.0249, respectively) and last 7 nights (7.6%; *P*=0.0468 and 8.0%; *P*=0.0371, respectively) of the Treatment Period.

The differences in the proportion of subjective sleep maintenance responders for LEM10 compared to ZOL and for LEM5 compared to ZOL over the first 7 nights and last 7 nights of the Treatment Period were not statistically significant.

Insomnia Severity Index

Total Score: The mean ISI total scores from items 1 to 7 for PBO, LEM10, LEM5, and ZOL were 19.4, 19.0, 18.9, and 19.2, respectively, at Baseline and decreased to 13.3, 11.1, 11.2, and 11.0, respectively, at Day 31, resulting in a mean change from baseline of –6.1, –7.9, –7.8, and –8.3, respectively. These decreases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –2.1; *P*<0.0001) and LEM5 compared to PBO (LS mean treatment difference –1.9; *P*=0.0001).

The treatment differences for change from baseline in ISI total scores from items 1 to 7 at Day 31 were not statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference 0.2; *P*=0.6412) or for LEM5 compared to ZOL (LS mean treatment difference 0.4; *P*=0.4466).

Daily Functioning Score: The mean Daily Functioning Scores from items 4 to 7 for PBO, LEM10, LEM5, and ZOL were 11.2, 10.8, 10.9, and 11.1, respectively, at Baseline and decreased to 7.3, 6.1, 6.1, and 5.9, respectively, at Day 31, resulting in a mean change from baseline of –3.9, –4.8, –4.8, and –5.2, respectively. These decreases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –1.1; *P*=0.0007) and LEM5 compared to PBO (LS mean treatment difference –1.1; *P*=0.0006).

The treatment differences for change from baseline in Daily Functioning Score from items 4 to 7 at Day 31 were not statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference 0.3; *P*=0.2744) or for LEM5 compared to ZOL (LS mean treatment difference 0.3; *P*=0.2951).

Fatigue Severity Scale

Average Score*:* The mean average FSS scores for PBO, LEM10, LEM5, and ZOL were 4.2, 4.2, 4.2, and 4.1, respectively, at Baseline and decreased to 3.4, 3.3, 3.3, and 3.3, respectively, at Day 31, resulting in a mean change from baseline of –0.8, –0.9, –0.9, and –0.9, respectively. These decreases were similar and not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –0.1; *P*=0.2745) and LEM5 compared to PBO (LS mean treatment difference –0.1; *P*=0.2348).

The treatment differences for change from baseline in mean average FSS scores at Day 31 were not statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference –0.03; *P*=0.7854) or for

LEM5 compared to ZOL (LS mean treatment difference –0.04; *P*=0.7110).

Total Sum Score: The mean total sum FSS scores for PBO, LEM10, LEM5, and ZOL were 37.5, 37.4, 37.5, and 37.2, respectively, at Baseline and decreased to 30.6, 29.5, 29.5, and 30.0, respectively, at Day 31, resulting in a mean change from baseline of –6.8, –8.0, –8.1, and –7.8, respectively. These decreases were larger and not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –1.2; *P*=0.2745) and LEM5 compared to PBO (LS mean treatment difference –1.3; *P*=0.2348).

The treatment differences for change from baseline in mean total sum FSS scores at Day 31 were not statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference –0.3; *P*=0.7854) or for LEM5 compared to ZOL (LS mean treatment difference –0.4; *P*=0.7110).

Exploratory Efficacy/Pharmacodynamic Results

Rebound Insomnia

At the 1st, 2nd, and 3rd days, the mean of the first 3 days, the mean of the 1st week, and the mean of the 2nd week of the Follow-up Period, there was no evidence for rebound insomnia in the LEM5 or LEM10 treatment groups for either sSOL or sWASO. That is, the upper bound of the 95% CI for both sSOL and sWASO following discontinuation of treatment did not overlap with the lower bound of the 95% CI at Baseline at any time point evaluated. Thus, sleep was not worse than before treatment as a result of having taken and then discontinued study drug. As defined in the SAP, these results are interpreted as a lack of strong evidence for rebound insomnia in the ZOL treatment group for either sSOL or WASO.

Taken together, these results indicate that while there was not strong evidence for rebound insomnia in any of the active treatment groups, there was some evidence of rebound insomnia, particularly for sSOL, in the ZOL treatment group.

In each treatment group, the majority of subjects did not have sSOL or sWASO that was 5 minutes longer at each time point during the Follow-up Period than at Baseline (last 7 nights before the screening PSG).

It is of note that the proportion of subjects who had sSOL that was 5 or more minutes longer during the Follow-up Period was, at all time points evaluated, numerically higher in the ZOL treatment group than the proportions in the PBO, LEM5, and LEM10 treatment groups.

Morning Sleepiness Item of the Sleep Diary

The mean ratings on the morning sleepiness question from the Sleep Diary for PBO, LEM10, LEM5, and ZOL were 4.2, 4.0, 4.1, and 4.3, respectively, at Baseline and increased to 4.7, 4.8, 4.9, and 5.1, respectively, over the first 7 mornings of the Treatment Period, resulting in a mean change from baseline of 0.5, 0.8, 0.8, and 0.8, respectively. These increases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 0.3; *P*=0.0217) and LEM5 compared to PBO (LS mean treatment difference 0.3; *P*=0.0151).

Over the last 7 mornings of the Treatment Period, the mean ratings on the morning sleepiness question from the Sleep Diary for PBO, LEM10, LEM5, and ZOL increased from baseline to 5.0, 5.2, 5.4, and 5.4, respectively, resulting in a mean change from baseline of 0.9, 1.2, 1.2, and 1.1, respectively. These increases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 0.3; *P*=0.0182) and LEM5 compared to PBO (LS mean treatment difference 0.4; *P*=0.0027).

The treatment differences for the change from baseline in the rating on the morning sleepiness question over the first 7 mornings and last 7 mornings of the Treatment Period were not statistically significant between LEM10 and ZOL and between LEM5 and ZOL.

The mean ratings on the morning sleepiness question from the Sleep Diary for PBO, LEM10, LEM5, and ZOL increased from baseline to 5.0, 5.0, 5.0, and 5.0, respectively, over the first 7 mornings of the Follow-up Period, resulting in a mean change from baseline of 0.8, 1.0, 0.8, and 0.7, respectively. These increases were not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 0.1; *P*=0.3544) and LEM5 compared to PBO (LS mean treatment difference 0.04; *P*=0.7312).

Over the last 7 mornings of the Follow-up Period, the mean ratings on the morning sleepiness question from the Sleep Diary for PBO, LEM10, LEM5, and ZOL increased from Baseline to 5.0, 4.9, 5.0, and 5.0, respectively, resulting in a mean change from baseline of 0.8, 0.9, 0.8, and 0.7, respectively. These increases were not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 0.03; *P*=0.8208) and LEM5 compared to PBO (LS mean treatment difference 0.09; *P*=0.4740).

The treatment differences for the change from baseline in the rating on the morning sleepiness question over the first 7 mornings and last 7 mornings of the Follow-up Period were not statistically significant between LEM10 and ZOL and between LEM5 and ZOL.

Sleep Architecture

The minutes and proportion of both NREM and REM sleep per TIB were increased for all sleep stages in both lemborexant doses, at both the beginning (Days 1/2) and end (Days 29/30) of treatment. These increases in NREM and REM sleep were statistically significantly greater for both LEM10 and LEM5 compared to PBO at both Days 1/2 and Days 29/30. Specifically, the change from baseline in both the minutes and proportion per TIB of NREM stages N1 and N2, and REM were statistically significantly different for both LEM10 and LEM5 compared to PBO at both time points. In addition, NREM stage N3 was significantly higher for LEM5 compared to PBO at Days 1/2. In parallel to the increases in NREM and REM sleep, corresponding decreases in total wake time were observed as well. As a proportion of TST, both NREM and REM were statistically significantly increased in both lemborexant doses compared to PBO at both Days 1/2 and Days 29/30, with the increases due primarily to increases in the proportion of REM sleep per TST.

Compared to ZOL, there were statistically significant increases in both the minutes and proportion per TIB of NREM sleep at Days 29/30 (but not Days 1/2), as well as increases in the minutes and proportion per TIB of REM sleep at both Days 1/2 for LEM5 and at Days 29/30 for both LEM5 and LEM10. In addition, there were small but statistically significant increases in the minutes and proportion of NREM stage N1 at both Days 1/2 and Days 29/30. There were also statistically significant differences for N2 and N3 per TIB for LEM5 (days 29/30) and LEM10 (Days 1/2) such that values for ZOL were higher. As a proportion of TST, both NREM and REM were statistically significantly increased in both lemborexant doses compared to ZOL at Days 1/2 and Days 29/30 with the increases due primarily to increases in the proportion of REM sleep per TST.

The latency to REM sleep was significantly decreased in both LEM10 and LEM5 compared to both PBO and ZOL at Days 1/2 and Days 29/30. Numerically, the decrease in REM latency was higher at the beginning relative to the end of treatment.

Awakenings: Number of Awakenings After Persistent Sleep

The mean number of awakenings after persistent sleep for PBO, LEM10, LEM5, and ZOL was 11.8, 11.6, 11.3, and 11.7, respectively, at Baseline, and decreased to 10.8, 11.2, 11.0, and 9.7 at Days 1/2, resulting in a mean change from baseline of –1.0, –0.4, –0.3, and –2.0, respectively. These changes were not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 0.5; P=0.1519) and LEM5 compared to PBO (LS mean treatment difference 0.5; P=0.1669).

The mean number of awakenings after persistent sleep for PBO, LEM10, LEM5, and ZOL changed from baseline to 10.6, 13.2, 12.2, and 10.2, respectively, at Days 29/30, resulting in a mean change from baseline of –1.4, 1.6, 0.9, and –1.5. These increases were larger and statistically significantly different for LEM10 compared to PBO (LS mean treatment difference 2.8; P<0.0001) and LEM5 compared to PBO (LS mean treatment difference 2.0; P<0.0001).

The treatment differences for change from baseline in mean number of awakenings after persistent sleep at Days 1/2 and Days 29/30 were larger and statistically significantly different for LEM10 compared to ZOL (Days 1/2, LS mean treatment difference 1.5; P<0.0001; Days 29/30, LS mean treatment difference 3.0; P<0.0001) and for LEM5 compared to ZOL (Days 1/2, LS mean treatment difference 1.5; P<0.0001; Days 29/30, LS mean treatment difference 2.2; P<0.0001).

Number of Long Awakenings After Persistent Sleep

The mean number of long awakenings after persistent sleep for PBO, LEM10, LEM5, and ZOL were 4.1, 4.4, 4.0, and 4.1, respectively, at Baseline, and decreased to 3.7, 2.7, 3.0, and 2.9, respectively, at Days 1/2, resulting in a mean change from baseline of –0.4, –1.6, –1.0, and –1.2, respectively. These decreases were statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –1.1; P<0.0001) and LEM5 compared to PBO (LS mean treatment difference –0.7; P<0.0001).

The mean number of long awakenings after persistent sleep for PBO, LEM10, LEM5, and ZOL decreased from baseline to 3.6, 3.5, 3.2, and 3.2, respectively at Days 29/30, resulting in a mean change from baseline of –0.6, –0.9, –0.8, and –1.0, respectively. These decreases were not statistically significantly different for LEM10 compared to PBO (LS mean treatment difference –0.2; P=0.2303) and were statistically significantly different for LEM5 compared to PBO (LS mean treatment difference –0.3; P=0.0464).

The treatment differences for change from baseline in mean number of long awakenings after persistent sleep at Days 1/2 were statistically significantly different for LEM10 compared to ZOL (LS mean treatment difference –0.3; *P*=0.0369) but not statistically significantly different at Days 29/30 (LS mean treatment difference 0.2; *P*=0.2135). The treatment differences at Days 1/2 and Days 29/30 were not statistically significantly different between LEM5 and ZOL (Days 1/2, LS mean treatment difference 0.1; *P*=0.4616; Days 29/30, LS mean treatment difference 0.1; *P*=0.6878).

Awakenings: Duration of Long Awakenings After Persistent Sleep

The mean duration of long awakenings decreased from baseline at both Days 1/2 and Days 29/30 for all treatment groups. The mean duration of long awakenings for PBO was 24.3 minutes at Baseline and decreased to 20.7 and 19.1 minutes at Days 1/2 and Days 29/30, respectively. For LEM10, the mean duration of long awakenings was 24.2 minutes at Baseline and decreased to 9.9 and 11.3 minutes at Days 1/2 and Days 29/30, respectively. For LEM5, the mean duration of long awakenings was 25.7 minutes at Baseline and decreased to 11.9 and 12.2 minutes at Days 1/2 and Days 29/30, respectively. For ZOL, the mean duration of long awakenings was 23.3 minutes at Baseline and decreased to 14.9 and 14.7 minutes at Days 1/2 and Days 29/30, respectively.

The treatment differences for change from baseline in duration of long awakenings were statistically significant compared to PBO at Days 1/2 for both LEM10 (LS mean treatment difference –10.8 minutes; *P*<0.0001) and LEM5 (LS mean treatment difference –8.9 minutes; *P*<0.0001) and at Days 29/30 for both LEM10 (LS mean treatment difference –8.0 minutes; *P*<0.0001) and LEM5 (LS mean treatment difference –7.2 minutes; *P*<0.0001). Compared to ZOL, the treatment differences were statistically significant at Days 1/2 for both LEM10 (LS mean treatment difference –5.1 minutes; *P*<0.0001) and LEM5 (LS mean treatment difference –3.1 minutes; *P*=0.0007) and Days 29/30 for both LEM10 (LS mean treatment difference –3.5 minutes; *P*=0.0006) and LEM5 (LS mean treatment difference –2.7 minutes; *P*=0.0083).

Additional Results Related to WASO

WASO1H

Mean WASO1H decreased from baseline at both Days 1/2 and Days 29/30 for all treatment groups.

WASO by Quarter of the Night

The mean WASO for the first 2 hours, second 2 hours, third 2 hours, and fourth 2 hours of the night decreased from baseline at both Days 1/2 and Days 29/30 for all treatment groups. Of note, the statistically significant decreases in WASO2H in the LEM10 and LEM5 treatment groups compared to ZOL at both Days 1/2 and Days 29/30 appear to be due primarily to effects of lemborexant on WASO in the final quarter of the night. That is, there were no substantial differences in the change from baseline in WASO between the ZOL and LEM10 or LEM5 treatment groups in the first, second or third quarters of the night. However, in the fourth quarter of the night, the differences between LEM10 and ZOL (Days 1/2: –19.1 vs –7.2 minutes, respectively; Days 29/30: –14.8 vs –5.9 minutes, respectively) and LEM5 and ZOL (Days 1/2: –14.6 vs –7.2 minutes, respectively; Days 29/30: –11.9 vs –5.9 minutes, respectively) are numerically larger than the other quarters of the night.

Additional Sleep Diary Variables – Sleep Quality

The treatment differences in the change from baseline in mean ratings on the quality of sleep question from the Sleep Diary were larger and statistically significantly different for LEM10 compared to PBO and LEM5 compared to PBO over the first 7 nights and last 7 nights of the Treatment Period.

There was no statistically significant treatment difference in the change from baseline for LEM10 and LEM5 compared to ZOL in the rating on the quality of sleep question from the Sleep Diary over the first 7 nights and last 7 nights of the Treatment Period.

Other Evaluations

For the EQ-5D-3L dimension of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, “no problems” were reported for the majority of subjects across all treatment groups at each time point. “Extreme problems” were reported for no more than 3 subjects per treatment group for any EQ-5D-3L domain.

The mean EQ VAS score increased from baseline at Day 31 for all treatment groups.

The treatment differences in the change from baseline in EQ VAS scores were larger and statistically significantly different for LEM10 compared to PBO at Day 31 (LS mean treatment difference 2.5; *P*=0.0072). The treatment difference in EQ VAS scores for LEM5 compared to PBO at Day 31 was not statistically

significant.

The treatment difference in the change from baseline in EQ VAS scores was larger and statistically significantly different for LEM10 compared to ZOL at Day 31 (3.1; P=0.0005). The treatment difference in EQ VAS scores for LEM5 compared to ZOL at Day 31 was not statistically significant.

PGI-Insomnia

For the PGI-insomnia, the analyses indicated that, compared to PBO, both LEM5 and LEM10 helped subjects sleep (42.4%, 64.2%, and 63.6% of subjects, respectively; comparisons with PBO P<0.05), reduced time to fall asleep (42.9%, 59.9%, and 65.2% of subjects, respectively; comparisons with PBO P<0.05), and increased TST (44.4%, 61.9%, and 62.1% of subjects, respectively; comparisons with PBO P<0.05). ZOL helped 72.1% of subjects sleep, reduced time to fall asleep for 63.1% of subjects, and increased TST for 70.9% of subjects; none of these proportions differed from LEM5 or LEM10, but were significantly greater than PBO for helping subjects sleep, reducing time to fall asleep, and increasing TST (P<0.05).

The appropriateness of treatment strength was selected as "just right" for 51.8% and 55.7% of subjects in the LEM5 and LEM10 treatment groups, respectively, compared to 39.4% of subjects in the PBO treatment group; and as "too strong" for 4.3%, 6.7%, and 1.0% of subjects, respectively; and as "too weak" for 44.0%, 37.5%, and 59.6% of subjects, respectively (comparisons with PBO P<0.05). The proportion of subjects who selected that the treatment strength was "just right" was similar across the LEM5, LEM10, and ZOL treatment groups (51.8%, 55.7%, and 52.0% of subjects, respectively).

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Pharmacokinetics

The concentrations of lemborexant and its metabolites following multiple dose administration were in the range of plasma concentrations in subjects from another study (E2006-A001-002) in which 5 or 10 mg multiple-dose lemborexant was administered. Population PK and PK/PD analyses integrating data from Study E2006-G000-304 and Study E2006-G000-303 will be summarized in a separate standalone report.

Pharmacodynamics

Postural Stability

Mean body sway upon awakening in the morning for PBO was 23.1 at Baseline and decreased to 20.8 and 22.2 at Days 2/3 and Days 30/31, respectively, resulting in a mean change from baseline of –2.0 and 1.7, respectively.

Mean body sway upon awakening in the morning for LEM5 was 26.4 at Baseline and decreased to 25.7 and 25.1 at Days 2/3 and Days 30/31, respectively, resulting in a mean change from baseline of –0.8 and –0.9, respectively. Mean body sway upon awakening in the morning for LEM10 was 23.7 at Baseline and changed to 24.4 and 22.8 at Days 2/3 and Days 30/31, respectively, resulting in a mean change from baseline of 0.6 and 0.5, respectively. These changes from baseline were not statistically significantly different for either LEM5 compared to PBO at Days 2/3 (LS mean treatment difference 2.5; P=0.1258) and Days 30/31 (LS mean treatment difference –0.7; P=0.6528), or for LEM10 compared to PBO at Days 2/3 (LS mean treatment difference 2.9; P=0.0741) and Days 30/31 (LS mean treatment difference –0.6; P=0.7161).

Mean body sway upon awakening in the morning for ZOL was 26.0 at Baseline and increased to 29.9 and 27.7 at Days 2/3 and Days 30/31, respectively, resulting in a mean change from baseline of 4.1 and 2.1, respectively.

The treatment differences for change from baseline in body sway upon awakening in the morning were statistically significantly lower for LEM5 compared to ZOL at Days 2/3 (LS mean treatment difference –4.7; P=0.0022) and for LEM10 compared to ZOL at Days 2/3 (LS mean treatment difference –4.3; P=0.0055). The treatment differences for change from baseline in body sway upon awakening in the morning for LEM5 compared to ZOL at Days 30/31 (LS mean treatment difference –2.7; P=0.0712) and LEM10 compared to ZOL at Days 30/31 (LS mean treatment difference –2.6; P=0.0890) were not statistically significant.

There was a statistically significant treatment difference for the change from baseline in body sway upon awakening in the morning for the ZOL treatment group compared to PBO at Days 2/3 (P<0.0001); however, this effect was not considered clinically meaningful as the change from baseline in the ZOL treatment group was less than 7 units. The treatment difference for change from baseline in body sway upon awakening in the morning for ZOL compared to PBO at Days 30/31 (LS mean treatment difference 1.99; P=0.2136) was not statistically significant.

Cognitive Performance Assessment Battery

Power of Attention

For power of attention, a lower value or a decrease from baseline indicates better performance. The threshold for clinically meaningful effects on power of attention, as estimated from the effects of alcohol on this measure, was designated as a LS mean change from baseline of 48.8 msec.

There were small but statistically significant treatment differences in the change from baseline in power of attention for LEM5 and LEM10 compared to PBO at Days 2/3 (LS mean treatment difference 30.8 msec; *P*=0.0141 and LS mean treatment difference 39.7 msec; *P*=0.0016, respectively) and Days 30/31 (LS mean treatment difference 43.3 msec; *P*=0.0086 and LS mean treatment difference 37.2 msec; *P*=0.0244, respectively).

For ZOL, the treatment differences in the change from baseline in power of attention were larger than for both lemborexant doses and were statistically significant compared to PBO at Days 2/3 (LS mean treatment difference 50.0 msec; *P*<0.0001) and Days 30/31 (LS mean treatment difference 43.7 msec; *P*=0.0086).

The treatment differences in the change from baseline in power of attention for LEM5 and LEM10 compared to ZOL at Days 2/3 and Days 30/31 were not statistically significant.

None of the statistically significant treatment differences were considered clinically meaningful, as no LS mean change from baseline values exceeded the threshold of 48.8 msec for any treatment group at either Days 2/3 or Days 30/31.

Quality of Memory

For quality of memory, a higher value or an increase from baseline indicates better performance. The threshold for clinically meaningful effects on quality of memory, as estimated from the effects of alcohol on this measure, was designated as a LS mean change from baseline of –32.6 units.

The treatment differences in the change from baseline in quality of memory for LEM5 and LEM10 compared to PBO at Days 2/3 and Days 30/31 were not statistically significant.

For ZOL, there was a decrease relative to baseline in quality of memory at both Days 2/3 and Days 30/31. The treatment difference in the change from baseline in quality of memory was statistically significant for ZOL compared to PBO at Days 2/3 (LS mean treatment difference –12.8 units; *P*=0.0023) but was not statistically significant at Days 30/31.

The treatment difference in the change from baseline in quality of memory was statistically significant for LEM5 compared to ZOL at Days 2/3 (LS mean treatment difference 12.7 units; *P*=0.0011), with LEM5 performing better than ZOL. The treatment differences in the change from baseline in quality of memory for LEM5 compared to ZOL at Days 30/31, and for LEM10 compared to ZOL at Days 2/3 and Days 30/31, were not statistically significant.

None of the statistically significant treatment differences were considered clinically meaningful, as no LS mean change from baseline values exceeded the threshold of –32.6 units for any treatment group at either Days 2/3 or Days 30/31.

Continuity of Attention

For continuity of attention, a higher value or an increase from baseline indicates better performance. The threshold for clinically meaningful effects on quality of memory, as estimated from the effects of alcohol on this measure, was designated as a LS mean change from baseline of –0.36 units.

The treatment differences in the change from baseline in continuity of attention for LEM5 and LEM10 compared to PBO at Days 2/3 and Days 30/31 were not statistically significant.

The treatment difference in the change from baseline in continuity of attention was statistically significantly different for ZOL compared to PBO at Days 2/3 (LS mean treatment difference –1.0 units; *P*=0.0088) but was not statistically significant at Days 30/31.

The treatment difference in the change from baseline in continuity of attention was statistically significantly different for LEM5 compared to ZOL at Days 2/3 (LS mean treatment difference 1.4 units; *P*=0.0002), with LEM5 performing better than ZOL. The treatment difference in the change from baseline in continuity of attention for LEM5 compared to ZOL at Days 30/31 was not statistically significant. The treatment differences in the change from baseline in continuity of attention for LEM10 compared to ZOL were not statistically significant at Days 2/3 or Days 30/31.

None of the statistically significant treatment differences were considered clinically meaningful, as no LS mean change from baseline values exceeded the threshold of –0.36 units for any treatment group at either Days 2/3 or Days 30/31.

Speed of Memory Retrieval

For speed of memory retrieval, a lower value or a decrease from baseline indicates better performance. The threshold for clinically meaningful effects on quality of memory, as estimated from the effects of alcohol on this measure, was designated as a LS mean change from baseline of 19.3 msec.

The treatment differences in the change from baseline in speed of memory retrieval for LEM5 compared to PBO and LEM10 compared to PBO at Days 2/3 and Days 30/31 were not statistically significant.

For ZOL, there were increases from baseline in speed of memory retrieval. The treatment difference in the change from baseline in speed of memory retrieval was statistically significantly different for ZOL compared to PBO at Days 2/3 (LS mean treatment difference 232.2 msec; *P*=0.0001) and Days 30/31 (LS mean treatment difference 171.0 msec; *P*=0.0194).

The treatment difference in the change from baseline in speed of memory retrieval was statistically significant for LEM5 and LEM10 compared to ZOL at Days 2/3 (LS mean treatment difference –203.4 msec; *P*=0.0004 and LS mean treatment difference –181.3 msec; *P*=0.0016, respectively) and Days 30/31 (LS mean treatment difference –135.4 msec; *P*=0.0475 and LS mean treatment difference –218.2 msec; *P*=0.0014, respectively), with both doses of lemborexant performing better than ZOL in all instances.

There were large differences in LS mean change from baseline values for PBO, LEM5, and LEM10 relative to ZOL, which was the only treatment group to show a mean increase from baseline in speed of memory retrieval. However, none of the statistically significant treatment differences were considered clinically meaningful, as the LS mean change from baseline in the ZOL treatment group did not reach the clinically meaningful threshold of an increase of 19.3 msec at either Days 2/3 or Days 30/31.

Pharmacogenomics

Not applicable.

Safety

In general, treatment-emergent adverse events (TEAEs) were reported for a similar proportion of subjects in the LEM10, LEM5 and PBO treatment groups, with TEAEs reported for a moderately higher proportion of subjects in the ZOL treatment group.

The majority of TEAEs in all treatment groups were of mild or moderate severity, with severe TEAEs reported for a small number of subjects in any treatment group. No severe TEAE was reported for any preferred term for more than 1 subject in any treatment group.

The most commonly reported TEAEs during the Treatment Period (reported for >2% of subjects in any lemborexant treatment group) were headache, somnolence, urinary tract infection, nasopharyngitis, and upper respiratory tract infection.

The rate of somnolence in LEM5 (4.1%) was approximately half the rate of somnolence in LEM10 (7.1%).

There were no deaths reported during this study. Serious TEAEs were reported for 2 subjects in the LEM5 treatment group and 4 subjects in the ZOL treatment group. No serious TEAEs were treatment-related.

Overall, TEAEs leading to discontinuation of study drug were uncommon.

Overall, no clinically notable findings for clinical laboratory tests, vital signs, or ECGs were deemed clinically significant, and no clinically notable trends in the data were observed (Listing 16.2.8.4 and Table 14.3.4.5.3).

Lemborexant was generally well-tolerated in the study population.

Conclusions

- In subjects age 55 years and older with insomnia disorder, lemborexant 5 mg and 10 mg met the primary and all key secondary objectives. There were highly statistically significant findings vs both PBO and ZOL on PSG efficacy endpoints. Both doses of lemborexant consistently demonstrated statistically significant treatment differences compared to PBO for the primary efficacy endpoint (change from baseline in LPS at Days 29/30) and for the key secondary efficacy endpoints (change from baseline in SE and WASO at Days 29/30). Statistically significant treatment differences for the key secondary efficacy endpoint, change from baseline in WASO2H at Days 29/30, were also demonstrated for both doses of lemborexant compared to ZOL.

Key PSG Findings for Lemborexant Versus Placebo

- There were statistically significantly greater decreases from baseline in LPS on Days 29/30 for both doses of lemborexant compared to PBO, indicating that lemborexant led to a shorter time to persistent sleep at the end of 1 month of treatment. The LSGM treatment ratio for LEM10 compared to PBO was 0.725 (P<0.001) and for LEM5 compared to PBO, was 0.773 (P=0.0003).

- There were statistically significantly greater increases from baseline in SE, and decreases from baseline in WASO and WASO2H on Days 29/30 for both doses of lemborexant compared to PBO, indicating improvement in sleep maintenance at the end of 1 month of treatment. For SE, the LS mean treatment difference for LEM10 compared with PBO was 8.0% (P<0.0001) and for LEM5 compared to PBO was 7.1% (P<0.0001). For WASO on Days 29/30, the LS mean treatment difference for LEM10 compared to PBO was -25.4 minutes (P<0.0001) and for LEM5 compared to PBO, it was –24.0 minutes (P<0.0001). For WASO2H, the LS mean treatment difference for LEM10 compared to PBO was –17.8 minutes (P<0.0001) and for LEM5 compared to PBO, it was -16.4 minutes (P<0.0001).

- There were statistically significantly greater decreases from baseline in LPS, increases from baseline in SE, and decreases from baseline in WASO and WASO2H on Days 1/2 for both doses of lemborexant compared to PBO, indicating that shorter time to persistent sleep and improvement in sleep maintenance compared to PBO were observed after the first 2 doses. For LPS, the LSGM treatment ratio for LEM10 compared to PBO on Days 1/2 was 0.792 (P=0.0002), and for LEM5 compared to PBO, it was 0.850 (P=0.0092). For SE, the LS mean treatment difference for LEM10 compared to PBO was 11.6% (P<0.0001), and for LEM5 compared to PBO, it was 9.0% (P<0.0001). For WASO, the LS mean treatment difference for LEM10 compared to PBO was –42.3 minutes (P<0.0001), and for LEM5 compared to PBO, it was –33.4 minutes (P<0.0001). For WASO2H, the LS mean treatment difference for LEM10 compared to PBO was –28.3 minutes (P<0.0001), and for LEM5 compared to PBO, it was –21.7 minutes (P<0.0001).

- There were statistically significantly greater increases from baseline in TST on both Days 1/2 and Days 29/30 for both doses of lemborexant compared to PBO, indicating more time spent asleep. The LS mean treatment difference for LEM10 compared to PBO was 56.9 minutes (P<0.0001) on Days 1/2 and 38.9 minutes (P<0.0001) on Days 29/30. The LS mean treatment difference for LEM5 compared to PBO was 44.1 minutes (P<0.0001) on Days 1/2, and 34.2 minutes (P<0.0001) on Days 29/30.

Key PSG Findings for Lemborexant Versus Zolpidem

- There were statistically significantly greater decreases from baseline in LPS, increases from baseline in SE and TST, and decreases from baseline in WASO and WASO2H on Days 1/2 and Days 29/30 for both doses of lemborexant compared to ZOL, indicating that shorter time to persistent sleep, improvement in sleep maintenance, and more time spent asleep compared to ZOL were observed after both the first 2 doses and at the end of 1 month of treatment. For LPS, the LSGM treatment ratio for LEM 10 compared to ZOL was 0.818 (P=0.0006) on Days 1/2 and 0.594 (P<0.0001) on Days 29/30; for LEM5 compared to ZOL, it was 0.874 (P=0.0218) on Days 1/2 and 0.634 (P<0.0001) on Days 29/30. For SE, the LS mean treatment difference for LEM10 compared to ZOL was 4.6% (P<0.0001) on Days 1/2, and 4.9% (P<0.0001) on Days 29/30; for LEM5 compared to ZOL, it was 2.1% (P=0.0011) on Days 1/2 and 3.9% (P<0.0001) on Days 29/30. For WASO, the LS mean treatment difference for LEM10 compared to ZOL was –15.1 minutes (P<0.0001) on Days 1/2 and –9.1 minutes (P=0.0016) on Days 29/30; for LEM5 compared to ZOL, it

was -6.2 minutes (P=0.0154) on Days 1/2, and –7.7 minutes (P=0.0073) on Days 29/30. For WASO2H, the LS mean treatment difference for LEM10 compared to ZOL was -13.1 minutes (P<0.0001) on Days 1/2 and -8.0 minutes (P=0.0005) on Days 29/30; for LEM5, it was –6.5 minutes (P=0.0020) on Days 1/2 and -6.7 minutes (P<0.0038) on Days 29/30.

Key Sleep Diary Findings for Lemborexant Versus Placebo

- Based on the Sleep Diary Handling Rules, there were statistically significantly greater decreases from baseline in sSOL, increases from baseline in sSE and sTST, and decreases from baseline in sWASO over the first 7 nights and last 7 nights of 1 month of treatment for both doses of lemborexant compared to PBO, indicating that subjects reported shorter time to sleep onset, improvement in sleep maintenance, and more time spent asleep compared to PBO at both the beginning and end of 1 month of treatment. For sSOL, the LSGM treatment ratio for LEM10 compared to PBO was 0.753 (P<0.0001) over the first 7 nights, and 0.689 (P<0.0001) over the last 7 nights of the Treatment Period; for LEM5 compared to PBO the LSGM treatment ratio was 0.815 (P<0.0001) over the first 7 nights, and 0.750 (P<0.0001) over the last 7 nights of the Treatment Period. For sSE, the LS mean treatment difference for LEM10 compared to PBO 6.8% (P<0.0001) over the first 7 nights, and 7.2% (P<0.0001) over the last 7 nights of the Treatment Period; for LEM5 compared to PBO, the LS mean treatment difference was 3.8% (P=0.0008) over the first 7 nights, and 4.6% (P=0.0005) over the last 7 nights of the Treatment Period. For sTST, the LS mean treatment difference for LEM10 compared to PBO was 34.5 minutes (P<0.0001) over the first 7 nights, and 37.8 minutes (P<0.0001) over the last 7 nights of the Treatment Period; for LEM5 compared to PBO the LS mean treatment difference was 19.1 minutes (P=0.0007) over the first 7 nights, and 23.6 minutes (P=0.0003) over the last 7 nights of the Treatment Period. For sWASO, the LS mean treatment difference for LEM10 compared to PBO was –26.3 minutes (P<0.0001) over the first 7 nights, and 20.6 minutes (P=0.0002) over the last 7 nights of the Treatment Period; for LEM5 compared to PBO, the LS mean treatment difference was –12.4 minutes (P=0.0093) over the first 7 nights, and –11.5 minutes (P=0.0396) over the last 7 nights of the Treatment Period.

Key Sleep Diary Findings for Lemborexant Versus Zolpidem

- Based on the Sleep Diary Handling Rules, there were statistically significant decreases from baseline in sSOL over the first 7 nights and last 7 nights of 1 month of treatment for both doses of lemborexant compared to ZOL. For sSOL, the LSGM treatment ratio for LEM10 compared to ZOL was 0.830 (P<0.0001) over the first 7 nights, and 0.811 (P<0.0001) over the last 7 nights of the Treatment Period; for LEM5 over the first 7 nights (LSGM treatment ratio 0.898; P=0.0122) and last 7 nights (LSGM treatment ratio 0.882; P=0.0176) of the Treatment Period.

- Based on the Sleep Diary Handling Rules, the increases from baseline in sSE and sTST over the first 7 nights and last 7 nights of 1 month of treatment were not statistically significant different for either dose of lemborexant compared to ZOL.

- Based on the Sleep Diary Handling Rules, the decreases in sWASO over the first 7 nights and last 7 nights of 1 month of treatment were not statistically significant different for LEM10 compared to ZOL. The decrease in sWASO over the first 7 nights of 1 month of treatment was not statistically significant different for LEM5 compared to ZOL, but there was a statistically significant difference for ZOL compared to LEM5 over the last 7 nights of 1 month of treatment, with ZOL showing a greater decrease.

Responder Analyses

- Objective Sleep Onset: There were no statistically significant differences in the proportion of responders on LPS for either dose of lemborexant compared to PBO after either the first 2 doses or at the end of 1 month of treatment. The difference in the proportion of responders on LPS was significantly higher for LEM10 compared to ZOL after the first 2 doses, as well as for LEM5 compared to ZOL at the end of 1 month of treatment. Of note is that approximately 40% of subjects were not eligible for this responder analysis as they did not meet the criterion for LPS greater than 30 minutes at Baseline.

- Subjective Sleep Onset: The difference in the proportion of responders on sSOL was significantly higher for both doses of lemborexant compared to PBO after both the first 2 doses and at the end of 1 month of

treatment. There were no statistically significant differences in the proportion of responders on sSOL for either dose of lemborexant compared to ZOL after the first 2 doses. The difference in the proportion of responders on sSOL was significantly higher for both doses of lemborexant compared to ZOL at the end of 1 month of treatment. Of note is that approximately 25% of the subjects were not eligible for this responder analysis as they did not meet the criterion for sSOL greater than 30 minutes at Baseline.

- Objective Sleep Maintenance: The difference in the proportion of responders on WASO was significantly higher for both doses of lemborexant compared to PBO after both the first 2 doses and at the end of 1 month of treatment. The difference in the proportion of responders on WASO was significantly higher for LEM10 compared to ZOL after both the first 2 doses and at the end of 1 month of treatment, and for LEM5 compared to ZOL at the end of 1 month of treatment. There were no statistically significant differences in the proportion of responders on WASO for LEM5 compared to ZOL after the first 2 doses.
- Subjective Sleep Maintenance: The difference in the proportion of responders for sWASO was significantly higher for both doses of lemborexant compared to PBO after both the first 2 doses and at the end of 1 month of treatment. There were no statistically significant differences in the proportion of responders for either dose of lemborexant compared to ZOL after either the first 2 doses or at the end of 1 month of treatment.

Other Efficacy Analyses

- There were statistically significant greater decreases from baseline in total ISI score at the end of 1 month of treatment for both doses of lemborexant compared to PBO. The decreases from baseline were not statistically significantly different for either dose of lemborexant compared to ZOL.
- There were statistically significant greater decreases from baseline in scores on the Daily Functioning items on the ISI at the end of 1 month of treatment for both doses of lemborexant compared to PBO. The decreases from baseline were not statistically significantly different for either dose of lemborexant compared to ZOL.
- The decreases from baseline in total and average FSS scores at the end of 1 month of treatment were not statistically significantly different for either dose of lemborexant compared to either PBO or ZOL.
- Subgroup analyses of PSG and Sleep Diary data indicated that, overall, the efficacy of lemborexant was similar across age and sex subgroups. For older males, the decrease from baseline in LPS was not different for LEM10 and PBO, a finding that should be interpreted with caution given the relatively small number of older males in the study.

Rebound Insomnia

- There was a lack of strong evidence of rebound insomnia during the 2 weeks following 1 month of treatment with either lemborexant or zolpidem. Nonetheless, there was some evidence for rebound insomnia in the ZOL treatment group, particularly for sSOL.

Morning Residual Sleepiness

- There was a small but statistically significant treatment difference in the increase from baseline in the rating on the morning sleepiness question from the Sleep Diary for both doses of lemborexant compared to PBO over the first 7 mornings and last 7 mornings of the Treatment Period ($P<0.05$), indicating slightly higher levels of alertness in LEM5 and LEM10.
- There were no statistically significant treatment differences for the change from baseline in the rating on the morning sleepiness question from the Sleep Diary for either dose of lemborexant compared to ZOL over the first 7 mornings and last 7 mornings of the Treatment Period, indicating similar increases in alertness in all active treatment groups.
- The treatment differences for the change from baseline in the rating on the morning sleepiness question from the Sleep Diary for both doses of lemborexant compared to both PBO and ZOL over the first 7 mornings and last 7 mornings of the Follow-up Period were not statistically significant.

Sleep Stage Architecture and Other PSG Variables

- Both doses of lemborexant increased both NREM and REM minutes and proportion of NREM and REM per TIB. The increases in REM sleep were statistically significantly greater for both doses of lemborexant compared to both PBO and ZOL at both the beginning and end of treatment. The increase in minutes and proportion of REM sleep resulted in slight decreases in NREM as a proportion of TST, with statistically significantly greater increases in REM sleep as a percentage of TST compared to both PBO and ZOL at both the beginning and end of treatment.
- Both doses of lemborexant shortened the latency to REM sleep at both the beginning and end of treatment compared to both PBO and ZOL, but more so at the beginning of treatment.
- The number of awakenings (defined as 1 minute or longer) decreased in all treatment groups but these changes were small. The number of long awakenings (defined as 5 minutes or longer) also decreased in all treatment groups and the treatment difference in the change from baseline was statistically significant for both doses of lemborexant compared to both PBO and ZOL. The duration of long awakenings decreased in both the lemborexant and ZOL treatment groups compared to PBO but the decrease in LEM5 and LEM10 was statistically significantly greater than that with ZOL at both the beginning and end of treatment.
- Mean WASO1H decreased from baseline at the beginning and end of treatment for all treatment groups.
- The decreases in WASO in each quarter of the night were numerically larger in both lemborexant treatment groups compared to PBO. Relative to ZOL, the differences in WASO were most apparent during the last quarter (ie, last 2 hours) of the night.

Additional Efficacy Variables

- The change from baseline in the Quality of Sleep rating was significantly higher for both doses of lemborexant and ZOL vs PBO over the first 7 nights and last 7 nights of the Treatment Period. Neither dose of lemborexant was significantly different from ZOL.
- There were no notable deficits in any of the EQ-5D-3L dimensions at Baseline, and no observed impact of treatment on the EQ-5D-3L dimensions.
- The PGI-Insomnia analyses indicated that, relative to PBO, more subjects in the LEM5 or LEM10 treatment groups reported a positive vs a neutral or negative medication effect with regards to helping subjects sleep, reducing time to fall asleep, and total time spent asleep. In addition, relative to PBO, more subjects in the LEM5 or LEM10 treatment groups reported that the strength of the medication was "just right" as opposed to "too weak" or "too strong".

Pharmacokinetic Conclusions

- The concentrations of lemborexant and its metabolites in this study were in the range of plasma concentrations from healthy subjects administered 5 or 10 mg when dosed at steady state. A standalone PK/PD report will summarize PK and exposure-response relationships.

Next-Morning Residual Effects

- Postural Stability: When postural stability was assessed immediately upon awakening, there was no statistically significant treatment difference in body sway for either lemborexant treatment group compared to PBO at either the beginning or end of treatment. In contrast, after the first 2 doses of zolpidem there was an increase in body sway that was statistically significantly different from PBO and both doses of lemborexant. After the last 2 doses, the treatment difference in the increase from baseline in body sway for ZOL was still significantly different from PBO. But at neither time point did the increase from baseline in body sway meet the clinically meaningful threshold.
- Cognitive Performance: There was a statistically significant treatment difference in the change from baseline in: the power of attention domain for both doses of lemborexant compared to PBO at both

Days 2/3 and Days 30/31, indicating relatively slower performance in the lemborexant treatment groups. There were statistically significant differences for ZOL compared to PBO on all 4 cognitive PAB domains at Days 2/3, and both power of attention and speed of memory retrieval on Days 30/31. The statistically significant treatment difference in the quality of memory and continuity of attention domains for LEM5 compared to ZOL at Days 2/3; and the speed of memory retrieval domain for both doses of lemborexant compared to ZOL at Days 2/3 and Days 30/31 indicated better performance for lemborexant relative to ZOL on these domains. Despite the pattern of worse performance for ZOL relative to the PBO and lemborexant treatment groups, particularly LEM5, none of the statistically significant results were considered clinically meaningful, based on the magnitude of effect of alcohol on these cognitive performance domains.

Safety

- In general, TEAEs were reported for a similar proportion of subjects in the LEM10, LEM5 and PBO treatment groups, with TEAEs reported for a moderately higher proportion of subjects in the ZOL treatment group.
- The majority of TEAEs in all treatment groups were of mild or moderate severity, with severe TEAEs reported for a small number of subjects in any treatment group. No severe TEAE was reported for any PT for more than 1 subject in any treatment group.
- The most commonly reported TEAEs during the Treatment Period (reported for >2% of subjects in any lemborexant treatment group) were headache, somnolence, urinary tract infection, nasopharyngitis, and upper respiratory tract infection.
- There were no deaths reported during this study. Serious TEAEs were reported for 2 subjects in the LEM5 treatment group and 4 subjects in the ZOL treatment group. No serious TEAEs were treatment-related.
- Overall, TEAEs leading to discontinuation of study drug were uncommon.
- Overall, no clinically notable findings for clinical laboratory tests, vital signs, or ECGs were deemed clinically significant, and no clinically notable trends in the data were observed (Listing 16.2.8.4 and Table 14.3.4.5.3).
- Lemborexant was generally well-tolerated at both doses studied.

Date of Report

29 Nov 2018