# Supplementary Online Content

Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. *JAMA Netw Open.* 2019;2(12):e1918254. doi:10.1001/jamanetworkopen.2019.18254



This supplementary material has been provided by the authors to give readers additional information about their work.

**eAppendix 1.** Trial Protocol Amendments

The order of primary, key secondary, additional secondary, exploratory objectives, and related endpoints was updated to incorporate feedback from regulatory authorities (Protocol Amendment 3; 16 Jun 2017; Protocol Amendment 4; 5 Feb 2018).

**eAppendix 2.** Supplemental Methods

## PARTICIPANTS

*Inclusion Criteria*

1. Male age 65 years or older or female age 55 years or older at the time of informed consent
2. Meets the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition* criteria for Insomnia Disorder, as follows:
    a) Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the participant is not eligible)
    b) Frequency of complaint ≥ 3 times per week
    c) Duration of complaint ≥ 3 months
    d) Associated with complaint of daytime impairment
3. History of subjective wake after sleep onset (sWASO) typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
4. Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. Reports habitual bedtime, defined as the time the participant attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
6. Insomnia Severity Index (ISI) score ≥ 13
7. Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary before the second screening visit

8. Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary
9. Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary
10. Objective (polysomnography [PSG]) evidence of insomnia as follows:
    a) Wake after sleep onset (WASO) average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes
11. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
12. Willing not to start a behavioral or other treatment program for the treatment of insomnia during the participant's participation in the study

*Exclusion Criteria*

1. A current diagnosis of sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows:
    a. STOPBang score ≥5
    b. International Restless Legs Scale score ≥16
    c. Epworth Sleepiness Scale score >15 (scores of 11 to 15 require excessive daytime sleepiness to be recorded in participant's Medical History)
2. Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy

3. On the Munich Parasomnia Scale (MUPS), endorsed the item that corresponds to a history of sleep-eating or reports a history of sleep-related violent behavior, sleep-driving, or symptoms of another parasomnia that in the investigator's opinion make the participant unsuitable for the study
4. Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second screening visit
5. Beck Depression Inventory - II (BDI-II) score >19 at Screening
6. Beck Anxiety Index (BAI) score >15 at Screening
7. Habitually naps during the day more than 3 times per week
8. Is a female of childbearing potential. Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, and are postmenopausal without other known or suspected cause), or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
9. Excessive caffeine use that in the opinion of the investigator contributes to the participant's insomnia, or habitually consumes caffeine-containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study.
10. History of drug or alcohol dependency or abuse within approximately the previous 2 years
11. Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3 hours before bedtime for the duration of his/her participation in the study

12. Known to be positive for human immunodeficiency virus
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
14. A prolonged QT/QTcF interval (QTcF >450 milliseconds [ms]) as demonstrated by a repeated electrocardiogram (ECG) at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms)
15. Current evidence of clinically significant disease (e.g., cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal; severe hepatic impairment; renal including severe renal impairment; neurological including myasthenia gravis; psychiatric disease; or malignancy within the past 5 years other than adequately treated basal cell carcinoma) or chronic pain that in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments, including the ability to perform tasks on the cognitive performance assessment battery (PAB). Participants for whom a sedating drug would be contraindicated for safety reasons because of the participant's occupation or activities are also excluded.
16. Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night
17. Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessment, including the ability to perform the PAB.
18. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) administration during the Prerandomization Phase (i.e., answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS)

19. Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS)
20. Scheduled for surgery during the study
21. Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period).
22. Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (Run-in Period)
23. Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator
24. Transmeridian travel across more than 3 time zones in the 2 weeks before Screening, or between Screening and Baseline, or plans to travel across more than 3 time zones during the study
25. A positive drug test at Screening, Run-In, or Baseline, or unwilling to refrain from use of recreational drugs during the study
26. Hypersensitivity to lemborexant or zolpidem or to their excipients
27. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5× the half-life, whichever is longer preceding informed consent
28. Previously participated in any clinical trial of lemborexant

TRIAL PROCEDURES

At the first screening visit (Visit 1), informed consent was obtained after the study had been fully explained to each participant and before the conduct of any screening procedures or assessments. A medical, psychiatric, and sleep history interview was conducted, and included confirmation that the participant met diagnostic criteria for insomnia disorder, and further that the participant complained of difficulties with sleep maintenance or early morning awakening, or both. Screening assessments included the Insomnia Severity Index (ISI), as well as the Epworth Sleepiness Scale (ESS), the STOPBang Sleep Apnea Questionnaire, the International Restless Legs Scale (IRLS), and Munich Parasomnia Scale (MUPS), collectively called the Sleep Disorders Screening Battery (SDSB). Additional eligibility criteria were assessed and safety assessments were conducted.

Sleep diaries were completed on at least 7 consecutive mornings, and providing that the sleep diary entries indicated continued eligibility with regard to sleep timing, duration of time spent in bed, and frequency of nights with symptoms of insomnia, participants underwent the second screening visit. An 8-hour PSG recording was undertaken at the second screening visit to rule out moderate to severe sleep apnea, PLMS with arousals and other sleep disorders.

In the Run-in Period, to screen-out placebo responders, participants were dispensed placebo tablets to be taken every night, 5 minutes before bedtime for at least 7 consecutive nights. All participants took 2 tablets a day; a single lemborexant-matched placebo tablet and a single zolpidem-matched placebo tablet. Participants continued to complete the daily sleep diary to assess continued eligibility with regard to WASO, which was required to be ≥60 minutes on at least 3 of the 7 nights. Participants returned to the clinic for the first of 2 consecutive

nights, during which PSG was recorded from eligible participants. These PSGs during the Run-in Period served both to ensure eligibility and as the baseline for PSG-derived endpoints. Participants continued take placebo tablets until baseline. Baseline sleep diary variables are the mean of sleep diary data entered on the last 7 mornings before the first baseline PSG during the Run-In Period.

In the Baseline Period, participants were admitted to the clinic for assessment of ISI, Fatigue Severity Scale, and EuroQol-5 Dimension-3 Level questionnaire. Blood and urine samples were collected for routine safety assessments, an ECG was performed, and vital signs and weight were assessed. The eC-SSRS was also administered. Participants who completed the Baseline Period and continued to meet the eligibility criteria were randomized and began the Treatment Period.

All participants took 2 tablets a day; a single lemborexant or lemborexant-matched placebo tablet and a single zolpidem or zolpidem-matched placebo tablet. Placebo tablets were identical in appearance to their active drug counterparts to maintain blinding, but lemborexant and zolpidem tablets were distinct. Randomization was performed centrally and stratified by country and by age group (55 to 64 years; 65 years or older).

## MEASURES OF EFFICACY

### *Polysomnography*

In-lab attended PSG was performed using a 6-channel electroencephalogram, a 4-channel electrooculogram, electromyogram, and electrocardiogram. A thermistor, a nasal air pressure monitoring sensor, an oximeter, piezoelectric bands, and a body position sensor were also

applied. Polysomnography was scored per the AASM Manual for the Scoring of Sleep and Associated Events.[1]

*Sleep Diary*

Electronic sleep diaries were based on the diary used in the phase 2 proof-of-concept/dose-finding study,[2] modified to be electronic with adjustments to the wording and instructions and with additional questions on alcohol use. Diaries were completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-up Period, and yielded several self-reported measures of sleep that were used to determine eligibility, as well as to assess efficacy and safety. Sleep parameters included subjective sleep onset latency (sSOL), subjective WASO (sWASO), subjective total sleep time (sTST), and subjective sleep efficacy (sSE). Participants' perception of quality of sleep on the previous night was assessed with the following question: "How would you rate the quality of your sleep last night?" Participants rated the quality of their sleep on a scale from 1 to 9, with 1 being extremely poor and 9 being extremely good. Sleep diaries were also used to assess subjective ratings of morning sleepiness with the following question: "How alert/sleepy do you feel this morning?" Participants rated their sleepiness or alertness level on a scale from 1 to 9, with 1 being extremely sleepy and 9 being extremely alert. Morning sleepiness was part of the electronic sleep diary, but was also asked verbatim at 1.5 hours after waketime on each morning that the participant attended the clinic following a PSG recording. Alcohol consumption that exceeded the daily maximum allowance of 2 alcoholic drinks or consumption within 3 hours of bedtime on the previous day was also recorded in the sleep diary.

*Rebound Insomnia via Sleep Diary*

Rebound insomnia was assessed during the Follow-up Period and was defined as worsened sleep (ie, higher value of sSOL or sWASO) relative to Screening after study drug treatment was completed. No rebound insomnia was suggested if the least-squares (LS) means for sSOL and sWASO for the Follow-up Period were all lower than for the Screening Period. Strong evidence of rebound insomnia was if the lower bound of the 95% CI of the treatment difference for sSOL or sWASO for each of the 3 nights, the mean of the first 3 nights, mean of the first 7 days, and mean of the second 7 nights of the Follow-up Period exceeded the upper bound of the 95% CI for the values during the Screening Period in the given treatment group. Rebound insomnia was also assessed at the individual participant level by identifying the proportion of participants in each treatment group whose sSOL or sWASO values were more than 5 minutes higher than at the participant's values during the Screening Period.

**eTable.** Summary of Sleep Onset and Sleep Maintenance End Points Measured by Sleep Diary at the Beginning (First 7 Nights) and End (Month 1) of Treatment by Treatment Group in Subjects Aged >55 Years With Insomnia Disorder

| | Placebo (n = 208) | Zolpidem ER 6.25 mg (n = 263) | Lemborexant 5 mg (n = 266) | Lemborexant 10 mg (n = 269) |
|---|---|---|---|---|
| **Subjective sleep onset latency (min)** | | | | |
| Baseline | | | | |
| Mean (SD)[a] | 55.9 (37.4) | 60.5 (36.4) | 65.8 (43.5) | 60.9 (42.5) |
| First 7 nights | | | | |
| Mean (SD)[b] | 48.9 (31.6) | 44.6 (27.6) | 42.4 (28.1) | 38.6 (32.1) |
| Mean (SD) change from baseline[c] | −6.8 (23.0) | −16.2 (29.5) | −22.5 (32.8) | −21.9 (29.3) |
| LSGM treatment difference vs placebo (95% CI)[c] | | 0.91 (0.83, 0.99) | 0.82 (0.75, 0.89) | 0.75 (0.69, 0.82) |
| *P* value[d] | | .03 | <.0001 | <.0001 |
| LSGM treatment difference vs ZOL (95% CI)[c] | | | 0.90 (0.83, 0.98) | 0.83 (0.76, 0.90) |
| *P* value[d] | | | .01 | <.0001 |
| Month 1 | | | | |
| Mean (SD)[e] | 47.6 (32.8) | 43.6 (30.6) | 38.8 (28.1) | 36.5 (31.1) |
| Mean (SD) change from baseline[f] | −8.1 (27.4) | −17.0 (30.7) | −25.2 (34.9) | −24.8 (34.1) |
| LSGM treatment difference vs placebo (95% CI)[f] | | 0.85 (0.76, 0.95) | 0.75 (0.67, 0.84) | 0.69 (0.62, 0.77) |
| *P* value[d] | | .004 | <.0001 | <.0001 |
| LSGM treatment difference vs ZOL (95% CI)[f] | | | 0.88 (0.80, 0.98) | 0.81 (0.73, 0.90) |
| *P* value[d] | | | .02 | <.0001 |
| **Subjective sleep efficiency (%)** | | | | |
| Baseline | | | | |
| Mean (SD)[g] | 56.1 (17.3) | 55.5 (15.8) | 56.1 (17.1) | 54.3 (18.3) |
| First 7 nights | | | | |
| Mean (SD)[h] | 62.5 (17.6) | 66.5 (16.4) | 66.0 (18.2) | 68.1 (18.4) |
| Mean (SD) change from baseline[i] | 6.7 (10.9) | 12.0 (12.5) | 10.6 (12.3) | 14.0 (14.2) |
| LSM treatment difference vs placebo (95% CI)[i] | | 5.1 (2.9, 7.4) | 3.8 (1.6, 6.0) | 6.8 (4.6, 9.0) |
| *P* value[d] | | <.0001 | <.001 | <.0001 |
| LSM treatment difference vs ZOL (95% CI)[i] | | | −1.4 (−3.5, 0.7) | 1.7 (−0.4, 3.8) |
| *P* value[d] | | | .20 | .11 |
| Month 1 | | | | |
| Mean (SD)[j] | 64.0 (19.2) | 69.5 (16.9) | 68.2 (19.3) | 69.9 (19.1) |
| Mean (SD) change from baseline[k] | 8.4 (13.3) | 14.8 (15.0) | 12.9 (13.9) | 16.1 (16.3) |
| LSM treatment difference vs placebo (95% CI)[k] | | 6.1 (3.5, 8.8) | 4.6 (2.0, 7.2) | 7.2 (4.6, 9.8) |
| *P* value[d] | | <.0001 | <.001 | <.0001 |

| | | | | |
|---|---|---|---|---|
| LSM treatment difference vs ZOL (95% CI)[k] | | | −1.5 (−4.0, 0.9) | 1.1 (−1.4, 3.5) |
| *P* value[d] | | | .22 | .40 |
| **Subjective wake after sleep onset (min)** | | | | |
| Baseline | | | | |
| Mean (SD)[l] | 170.9 (80.7) | 173.1 (77.2) | 166.8 (82.0) | 175.4 (83.5) |
| First 7 nights | | | | |
| Mean (SD)[m] | 143.5 (80.6) | 124.8 (75.3) | 127.4 (78.3) | 119.8 (74.8) |
| Mean (SD) change from baseline[n] | −27.9 (45.2) | −48.9 (51.8) | −39.3 (55.0) | −55.1 (66.7) |
| LSM treatment difference vs placebo (95% CI)[n] | | −20.5 (−29.9, −11.1) | −12.4 (−21.8, −3.1) | −26.3 (−35.7, −17.0) |
| *P* value[d] | | <.0001 | .009 | <.0001 |
| LSM treatment difference vs ZOL (95% CI)[n] | | | 8.1 (-0.7, 16.9) | −5.8 (-14.6, 3.0) |
| *P* value[d] | | | .07 | .19 |
| Month 1 | | | | |
| Mean (SD)[o] | 135.9 (85.0) | 109.6 (72.6) | 119.3 (81.6) | 117.1 (83.8) |
| Mean (SD) change from baseline[p] | −36.0 (57.6) | −63.5 (64.2) | −44.5 (58.1) | −58.0 (72.8) |
| LSM treatment difference vs placebo (95% CI)[p] | | −25.9 (−36.9, −14.9) | −11.5 (−22.4, −0.6) | −20.6 (−31.5, −9.6) |
| *P* value[d] | | <.0001 | .04 | <.001 |
| LSM treatment difference vs ZOL (95% CI)[p] | | | 14.5 (4.2, 24.7) | 5.4 (−4.9, 15.7) |
| *P* value[d] | | | .006 | .31 |

Abbreviations: ER, extended release; LSGM, least squares geometric mean; LSM, least squares mean; ZOL, zolpidem tartrate extended release 6.25 mg.

[a]Placebo, n = 206; zolpidem, n = 258; lemborexant 5 mg, n = 263; lemborexant 10 mg, n = 269.

[b]Placebo, n = 203; zolpidem, n = 256; lemborexant 5 mg, n = 261; lemborexant 10 mg, n = 266.

[c]Placebo, n = 202; zolpidem, n = 251; lemborexant 5 mg, n = 259; lemborexant 10 mg , n = 266.

[d]*P* values were based on using mixed-effect model repeated measurement analysis with factors of age group, region, treatment, visit (first 7 nights, last 7 nights [Month 1]), and treatment-by-visit interaction as fixed effects, and baseline value of the sleep variable of interest as a covariate. Missing values were not imputed and assumed to be missing at random. Owing to non-normal distribution of sSOL data, values were log-transformed, and statistical comparisons made based on the LSGM ratios.

[e]Placebo, n = 197; zolpidem, n = 251; lemborexant 5 mg, n = 254; lemborexant 10 mg, n = 258.

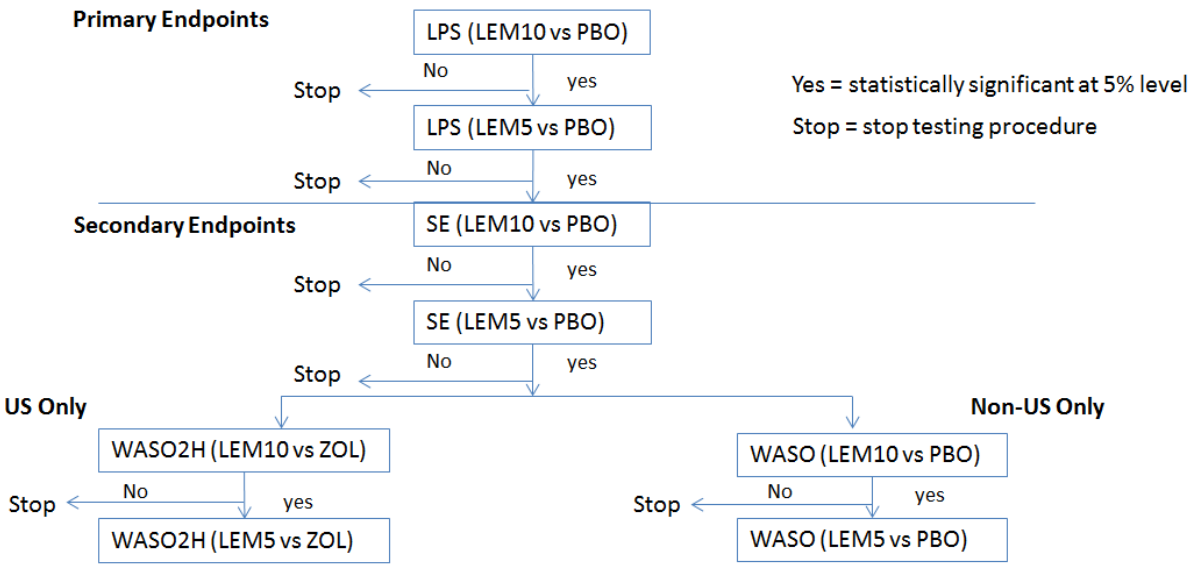
[f]Placebo, n = 196; zolpidem, n = 246; lemborexant 5 mg, n = 252; lemborexant 10 mg, n = 258.

[g]Placebo, n = 201; zolpidem, n = 247; lemborexant 5 mg, n = 253; lemborexant 10 mg, n = 258.

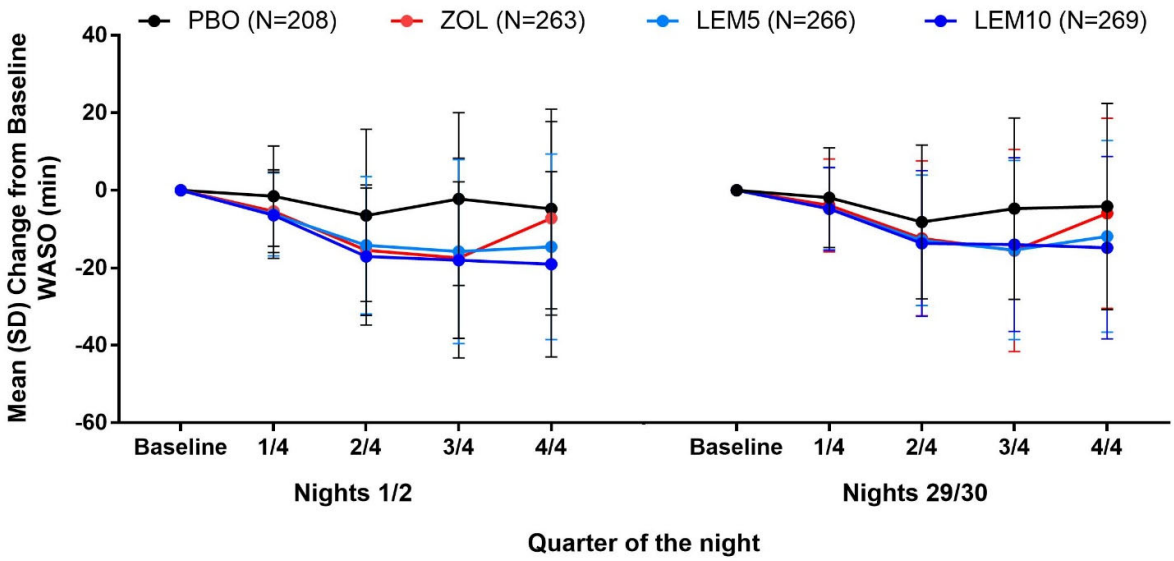
[h]Placebo, n = 201; zolpidem, n = 254; lemborexant 5 mg, n = 260; lemborexant 10 mg, n = 263.

[i]Placebo, n = 197; zolpidem, n = 240; lemborexant 5 mg, n = 251; lemborexant 10 mg, n = 254.
[j]Placebo, n = 195; zolpidem, n = 250; lemborexant 5 mg, n = 254; lemborexant 10 mg, n = 252.
[k]Placebo, n = 190; zolpidem, n = 235; lemborexant 5 mg, n = 245; lemborexant 10 mg, n = 244.
[l]Placebo, n = 206; zolpidem, n = 259; lemborexant 5 mg, n = 264; lemborexant 10 mg, n = 266.
[m]Placebo, n = 203; zolpidem, n = 257; lemborexant 5 mg, n = 262; lemborexant 10 mg, n = 264.
[n]Placebo, n = 202; zolpidem, n = 253; lemborexant 5 mg, n = 261; lemborexant 10 mg, n = 262.
[o]Placebo, n = 197; zolpidem, n = 251; lemborexant 5 mg, n = 254; lemborexant 10 mg, n = 255.
[p]Placebo, n = 196; zolpidem, n = 247; lemborexant 5 mg, n = 253; lemborexant 10 mg, n = 253.

**eFigure 1.** Flowchart of the Gate-Keeping Procedure for Handling Multiple Comparisons



**eFigure 2.** Change From Baseline WASO by Quarter of the Night




Abbreviations: PBO, placebo; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; WASO, wake after sleep onset; ZOL, zolpidem tartrate extended release 6.25 mg.

## eReferences


1. Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications: version 2.3. Darien, IL; American Academy of Sleep Medicine; 2016.
2. Murphy P, Moline M, Mayleben D, et al. Lemborexant, a dual orexin receptor antagonist (DORA) for the treatment of insomnia disorder: results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. *J Clin Sleep Med.* 2017;13(11):1289-1299.