SUPPORTING INFORMATION

APPENDIX S1. ENROLLMENT CRITERIA

Subjects were required to have regular sleep timing and duration, defined per the following criteria:

- Regular time in bed, between 7 and 9 hours as reported at Screening and verified by the Sleep Diary during the Screening Period before the adaptation night such that time in bed was not less than 7 hours or more than 9 hours on more than 2 of the 7 consecutive nights recorded in the Sleep Diary
- Regular bedtime, defined as the time the subject attempts to fall asleep, between 22:00 and 01:00 and regular wake time, defined as the time the subject gets out of the bed for the day, between 05:00 and 09:00 as reported at Screening and verified by the Sleep Diary during the Screening Period before the adaptation night such that neither bedtime nor wake time is outside of the permitted time-windows on more than 2 of the 7 consecutive nights.

Subjects were excluded if they had a current diagnosis of other sleep disorders, had subjective sleep onset latency > 20 minutes, or subjective wake after sleep onset > 60 minutes on more than 2 nights as reported on the Sleep Diary before the adaptation night. Latency to persistent sleep (LPS) > 30 minutes, as measured by polysomnography (PSG), or a sleep-onset rapid eye movement (REM) period, defined as first epoch of stage REM within 15 minutes of sleep onset were also exclusion criteria. After several subjects unexpectedly met the exclusion criterion of LPS > 30 minutes, a protocol amendment permitted repeat baseline PSG.

APPENDIX S2. CONCOMITANT DRUG/THERAPY

Subjects were advised to limit caffeine consumption to ≤ 4 cups of caffeinated beverages per day, or ≤ 400 mg caffeine per day. They were instructed to avoid caffeine after 15:00 on each of the 4 treatment days when they would spend the night in the sleep laboratory. Alcohol was permitted in limited quantities during the study. Subjects were not permitted to consume any alcohol on any of the days when they were to spend the night in the sleep laboratory. Centrally acting medications or

substances that are known to induce sleep were not permitted during the treatment periods. Drug classes that were prohibited included anticholinergics (centrally acting); antihistamines; anxiolytics with known sedating effects; hypnotics, herbal preparations with sedating effects; monoamine oxidase inhibitors; opioid analgesics; muscle relaxants with known sedating effects; and stimulants. Drugs that are moderate or strong inhibitors or inducers of CYP3A were not permitted for 1 week or 5 half-lives (whichever is longer) before the Baseline night and through the end of the study.

APPENDIX S3. ASSESSMENT DETAILS

Computerized Cognitive Performance Test Battery

Cognitive function was assessed with the Cognitive Drug Research computerized assessment system (Cambridge, UK).[1] The cognitive performance assessment battery (CPAB) comprised nine tasks including Simple Reaction Time, Choice Reaction Time, Digit Vigilance, Immediate Word Recall, Delayed Word Recall, Numerical Working Memory, Spatial Working Memory, Word Recognition, and Picture Recognition. The full CPAB took approximately 18 minutes to complete. Four composite domain factor scores were calculated by combining outcome variables from the various tests. The four domain factor scores are Power of Attention (lower scores are better), Continuity of Attention (higher scores are better), Quality of Memory (higher scores are better), and Speed of Memory Retrieval (lower scores are better).

While completing the assessment, subjects were in bed, in an upright position, with ambient lighting maintained at a level of 80–100 lux. On the evening of the Screening polysomnography (PSG) visit, before bedtime, subjects were introduced to the CPAB tasks and underwent a minimum of two training sessions. On the morning after the Screening PSG, subjects completed a session of the CPAB for familiarization purposes.

APPENDIX S4. STATISTICAL ANALYSES

For the secondary endpoint of the Power of Attention from the cognitive performance assessment battery (CPAB), 48 subjects had 98% power to detect a treatment difference of lemborexant (LEM) to zolpidem (ZOL) of 48.8 msec (standard deviation [SD] = 80), two-sided 0.05 test. The Quality of Memory from the CPAB had 86% power with 48 subjects to detect a treatment difference of LEM to ZOL of 32.57% (SD = 72), two-sided 0.05 test. These treatment differences in cognitive measures have been associated with a 0.5-g/kg dose of alcohol.[2] For the secondary endpoint of auditory awakening threshold, there was 97% power with 48 subjects to test for an 8-dB change from Baseline treatment difference of LEM to ZOL, SD = 14, two-sided 0.05 test. An 8-db change from baseline was considered the minimal clinically important difference, based on arousal thresholds after administration of flurazepam.[3-5]

Randomization

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

After the Baseline Period, subjects were randomized to one of four treatment sequence groups. The randomization number lists were sent to each site and were assigned to subjects by an unblinded pharmacist. Each subject received lemborexant 5 mg (LEM5), lemborexant 10 mg (LEM10), ZOL, and placebo (PBO), according to their assigned treatment sequence. No more than 14 subjects of either sex were assigned to a treatment sequence. Randomization was performed at each site. The randomization code was provided to each site, and the unblinded pharmacist assigned the subjects to the correct sequence.

Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff, were blinded to the treatment codes. There was an unblinded pharmacist at each site who prepared the study medication. Then the study medication was coded for each subject. Randomization data were kept strictly confidential, filed securely by an appropriate group with the sponsor, and accessible only to authorized persons until the time of unblinding, per the standard operating procedure. The study drug was provided to an unblinded pharmacist in an open-label manner. The unblinded pharmacist was responsible for dispensing in accordance with subject randomization in a blinded manner. Note that Eisai Clinical Trial Supplies personnel were also unblinded to the treatment codes.

A master list of all treatments and the subject numbers associated with them were maintained in a sealed envelope by the clinical supply vendor and by the sponsor. In addition, master code breaker reports or envelopes identifying the treatment group of each subject number were provided to the site and to the sponsor in sealed envelopes. These code breaker reports or envelopes were not to be opened unless an emergency occurred and knowledge of the subject's randomization code may have affected his/her medical treatment. ZOL- and LEM-matched PBO tablets were administered to maintain blinding.

APPENDIX S5. RESULTS

Auditory Awakening Threshold

Unexpectedly high numbers of subjects were already awake during the window from 4–4.5 hours postdose (n = 12, 6, 7, and 4 in the placebo, zolpidem [ZOL], lemborexant 5 mg [LEM5], and lemborexant 10 mg [LEM10] groups, respectively), despite being "good" sleepers based on entry criteria. For this reason, post hoc sensitivity analyses were performed limited to those awakened in

Stage N2, to assess the potential influence of sleep inertia. There were no differences among the treatments regarding the number of decibels required to awaken a subject in Stage N2; the mean (standard deviation) observed values across treatments ranged from 46.2 (18.3) dB in the LEM5 group to 49.4 (23.4) dB in the ZOL group.

Table S1—Baseline demographics and characteristics by treatment sequence.

	Sequence 1 (N = 16)	**Sequence 2 (N = 15)**	**Sequence 3 (N = 16)**	**Sequence 4 (N = 16)**
Age, years				
Mean	66.4 (7.1)	64.4 (6.2)	61.9 (4.7)	61.2 (5.7)
Median	66.0	63.0	62.0	60.5
Range	57–80	55–75	55–71	55–73
55–64 years, n (%)	5 (31.3)	8 (53.3)	11 (68.8)	11 (68.8)
≥ 65 years, n (%)	11 (68.8)	7 (46.7)	5 (31.3)	5 (31.3)
Male, n (%)	6 (37.5)	4 (26.7)	2 (12.5)	2 (12.5)
Female, n (%)	10 (62.5)	11 (73.3)	14 (87.5)	14 (87.5)
Race, n (%)				
White	12 (75.0)	7 (46.7)	11 (68.8)	9 (56.3)
Black or African American	3 (18.8)	6 (40.0)	5 (31.3)	4 (25.0)
Other	1 (6.3)	2 (13.3)	0	3 (18.8)
Auditory awakening threshold (4 hours), dB	46.1 (23.2)	53.5 (25.7)	47.3 (23.7)	45.4 (21.7)
Body sway[a]				
4 hours	19.5 (20.5)	20.6 (14.5)	23.6 (14.9)	29.0 (14.9)
8 hours	19.9 (15.7)	24.9 (20.5)	24.6 (16.5)	32.3 (22.6)
Power of Attention, msec				
4 hours	1377.8 (147.1)	1409.3 (132.3)	1379.4 (109.7)	1437.6 (188.8)
8 hours	1423.9 (205.9)	1450.1 (177.2)	1405.9 (150.0)	1501.6 (352.6)
Continuity of Attention, unit				
4 hours	92.6 (2.4)	92.2 (3.5)	91.1 (4.2)	92.4 (2.0)
8 hours	91.9 (2.9)	91.2 (2.6)	92.6 (2.8)	91.9 (2.6)
Quality of Memory, unit				
4 hours	346.4 (81.7)	341.0 (59.8)	373.6 (45.2)	382.6 (58.4)
8 hours	326.6 (73.3)	332.4 (54.8)	339.7 (66.9)	338.9 (69.5)
Speed of Memory Retrieval, msec)				
4 hours	5042.1 (1061.4)	4473.1 (814.1)	4523.0 (861.2)	4302.2 (814.7)
8 hours	4780.4 (963.4)	4576.3 (1027.3)	4630.1 (903.9)	4300.4 (710.4)

Data are mean (standard deviation) unless stated otherwise.

[a]A unit of body sway is defined as 1/3 degree angle of arc movement of the ataxiameter.

Sequences: 1=PBO/ZOL/LEM10/LEM5; 2=ZOL/LEM5/PBO/LEM10; 3=LEM5/LEM10/ZOL/PBO; 4=LEM10/PBO/LEM5/ZOL.

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PBO = placebo, ZOL = zolpidem tartrate extended release 6.25 mg.

Table S2—Sensitivity analysis: body sway after middle of the night awakening excluding subjects who were already awake.[a]

Group	n	Baseline	Postdose	Change from baseline	LSM difference from PBO (95% CI); p value[b]	LSM difference from ZOL (95% CI); p value[b]
PBO	27	24.9 (17.1)	23.6 (16.0)	-1.3 (12.9)		
ZOL	27		47.5 (35.2)	22.6 (29.9)	24.1 (15.5–32.6); p < 0.0001	
LEM5	27		26.3 (15.2)	1.3 (17.1)	2.7 (-5.8 to 11.3); p = 0.5276	21.3 (12.8–29.9); p < 0.0001
LEM10	27		31.9 (16.4)	7.0 (13.7)	8.6 (0.1–17.2); p = 0.0478	15.4 (6.9–24.0); p = 0.0005

Data are mean (standard deviation) unless stated otherwise.

[a]Subjects were asleep immediately before assessment at baseline in all treatment conditions.

[b]p values based on mixed-effect model repeated measurement analysis with treatment treatment, sequence, period, baseline (time-matched), time (h postdose), treatment × time, baseline × time as fixed effects, and time with subject as a random effect and a repeated effect for time, with subject within sequence. The treatment-by-time interaction is used to construct the treatment comparisons at a specific time.

CI = confidence interval; LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LSM = least squares mean; PBO = placebo,

ZOL = zolpidem tartrate extended release 6.25 mg.

Table S3—Change from baseline for cognitive performance assessment battery domains.

	PBO (n = 56)	ZOL (n = 56)	LEM5 (n = 56)	LEM10 (n = 56)
Power of Attention, msec				
4-hour baseline, mean (SD)	1407.0 (150.9)[b]			
LSM (SE) change from baseline 4 hours postdose	55.6 (40.3)	138.2 (40.3)	128.6 (40.3)	257.8 (40.3)
LSM difference from PBO (95% CI); p value[a]		82.6 (-18.9 to 184.0); p = 0.1104	73.0 (-28.5 to 174.5) p = 0.1579	202.2 (100.8–303.7) p = 0.0001
LSM difference from ZOL (95% CI); p value[a]			9.5 (-91.9 to 111.0); p = 0.8533	-119.7 (-221.1 to -18.2); p = 0.0210
8-hour baseline, mean (SD)	1450.5 (243.8)[b]			
LSM (SE) change from baseline 8 hours postdose	6.0 (40.2)	12.7 (40.2)	46.5 (40.2)	87.1 (40.2)
LSM difference from PBO (95% CI); p value[a]		6.7 (-94.7 to 108.2); p = 0.8963	40.5 (-61.0 to 142.0); p = 0.4332	81.1 (-20.4 to 182.6); p = 0.1168
LSM difference from ZOL (95% CI); p value[a]			-33.8 (-135.2 to 67.7) p = 0.5134	-74.4 (-175.9 to 27.1) p = 0.1504
Continuity of Attention, standard unit				
4-hour baseline, mean (SD)	92.0 (3.3)[b]			
LSM (SE) change from baseline 4 hours postdose	-0.3 (0.6)	-3.8 (0.6)	-1.5 (0.6)	-3.3 (0.6)
LSM difference from PBO (95% CI); p value[a]		-3.5 (-4.9 to -2.1); p < 0.0001	-1.1 (-2.5 to 0.3); p = 0.1142	-2.9 (-4.3 to -1.5); p < 0.0001
LSM difference from ZOL (95% CI); p value[a]			-2.4 (-3.8 to -1.0); p = 0.0009	-0.6 (-2.0 to 0.8); p = 0.4092
8-hour baseline, mean (SD)	91.8 (2.8)[b]			
LSM (SE) change from baseline 8 hours postdose	-0.8 (0.6)	-1.4 (0.6)	-0.7 (0.6)	-1.9 (0.6)
LSM difference from PBO (95% CI); p value[a]		-0.6 (-2.0 to 0.8); p = 0.4129	0.2 (-1.3 to 1.6); p = 0.8293	-1.1 (-2.5 to 0.4); p = 0.1409
LSM difference from ZOL (95% CI); p value[a]			-0.7 (-2.1 to 0.7);	0.5 (-0.9 to 1.9);

			p = 0.3011	p = 0.5122
Quality of Memory, standard unit				
4-hour baseline, mean (SD)	358.1 (65.9)[c]			
LSM (SE) change from baseline 4 hours postdose	12.8 (7.9)	-29.1 (7.9)	0.2 (7.9)	-21.8 (7.9)
LSM difference from PBO (95% CI); p value[a]		-41.9 (-59.7 to -24.0); p < 0.0001	-12.7 (-30.4 to 5.1); p = 0.1614	-34.6 (-52.3 to -16.8); p = 0.0001
LSM difference from ZOL (95% CI); p value[a]			-29.2 (-47.0 to -11.4); p = 0.0014	-7.3 (-25.1 to 10.5); p = 0.4211
8-hour baseline, mean (SD)	333.1 (66.2)[b]			
LSM (SE) change from baseline 8 hours postdose	-9.1 (7.9)	-0.8 (7.9)	-2.0 (7.9)	-2.6 (7.9)
LSM difference from PBO (95% CI); p value[a]		8.3 (-9.4 to 26.0); p = 0.3568	7.1 (-10.7 to 24.8); p = 0.4335	6.5 (-11.2 to 24.2); p = 0.4710
LSM difference from ZOL (95% CI); p value[a]			1.3 (-16.5 to 19.0); p = 0.8901	1.8 (-15.9 to 19.5); p = 0.8408
Speed of Memory Retrieval, msec				
4-hour baseline, mean (SD)	4,639.3 (943.8)[d]			
LSM (SE) change from baseline 4 hours postdose	-342.1 (100.5)	249.1 (101.2)	-128.4 (100.5)	-36.3 (100.5)
LSM difference from PBO (95% CI); p value[a]		591.2 (372.1–810.2); p < 0.0001	213.8 (-4.1 to 431.6); p = 0.0544	305.8 (88.0–523.6); p = 0.0061
LSM difference from ZOL (95% CI); p value[a]			377.4 (158.4–596.5); p = 0.0008	285.4 (66.3–504.5); p = 0.0108
8-hour baseline, mean (SD)	4,626.1 (905.1)[b]			
LSM (SE) change from baseline 8 hours postdose	-259.0 (100.5)	-128.5 (100.5)	-308.0 (100.5)	-275.0 (100.5)
LSM difference from PBO (95% CI); p value[a]		130.4 (-87.4 to 348.2); p = 0.2395	-49.1 (-266.9 to 168.8); p = 0.6581	-16.0 (-233.8 to 201.8); p = 0.8850
LSM difference from ZOL (95% CI); p value[a]			179.5 (-38.3 to 397.3); p = 0.1059	146.5 (-71.4 to 364.3); p = 0.1869

[a]p values based on mixed-effect model repeated measurement analysis with treatment, sequence, period, baseline (time-matched), time (h postdose), treatment × time, and baseline × time as fixed effects, and time with subject as a random effect and a repeated effect for time, with subject within sequence. Only subjects with complete data were included in this analysis.

[b]Baseline values presented for PBO were the same across groups for Power of Attention (4 and 8 hours), Continuity of Attention (4 and 8 hours), Quality of Memory (8 hours), and Speed of Memory Retrieval (8 hours)

[c]For ZOL, 4-hour baseline mean (SD) for Quality of Memory was 358.4 (66.4), assessed in 55 subjects.

[d]For ZOL, 4-hour baseline mean (SD) for Speed of Memory Retrieval was 4655.6 (944.5), assessed in 55 subjects.

Power of Attention: lower values reflect better performance; higher values reflect impairment.

Continuity of Attention: higher values reflect better performance; lower values reflect impairment.

Quality of Memory: higher values reflect better performance; lower values reflect impairment.

Speed of Memory Retrieval: lower values reflect better performance; higher values reflect impairment.

CI = confidence interval, LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LSM = least squares mean, PBO = placebo, SD = standard deviation, SE = standard error, ZOL = zolpidem extended release 6.25 mg.

Table S4—Change from baseline for cognitive performance assessment battery domains (MNAR analysis).

	PBO (n = 63)	ZOL (n = 63)	LEM5 (n = 63)	LEM10 (n = 63)
Power of Attention, msec				
4-hour baseline, mean (SD)	1404.9 (150.4)	1403.2 (150.4)	1401.9 (150.1)	1408.2 (148.3)
LSM (SE) change from baseline 4 hours postdose	55.3 (37.8)	130.6 (38.2)	127.0 (38.4)	251.2 (41.9)[†§]
8-hour baseline, mean (SD)	1448.2 (242.2)	1448.1 (239.1)	1444.8 (239.3)	1452.0 (239.8)
LSM (SE) change from baseline 8-hour postdose	6.5 (37.8)	2.3 (37.8)	46.8 (38.6)	88.6 (39.8)
Continuity of Attention, standard unit				
4-hour baseline, mean (SD)	92.0 (3.3)	92.0 (3.2)	92.0 (3.2)	92.0 (3.2)
LSM (SE) change from baseline 4 hours postdose	-0.3 (0.6)	-3.7 (0.6)*	-1.4 (0.6)[‡]	-3.1 (0.6)*
8-hour baseline, mean (SD)	91.8 (2.8)	91.8 (2.8)	91.8 (2.8)	91.8 (2.8)
LSM (SE) change from baseline 8 hours postdose	-0.7 (0.6)	-1.3 (0.6)	-0.6 (0.6)	-1.8 (0.6)
Quality of Memory, standard unit				
4-hour baseline, mean (SD)	358.2 (65.3)	358.1 (65.5)	358.7 (64.7)	360.2 (65.8)
LSM (SE) change from baseline 4 hours postdose	12.6 (7.6)	-25.9 (7.7)*	-1.4 (7.7)[‡]	-24.0 (7.7)*
8-hour baseline, mean (SD)	333.2 (65.6)	333.1 (65.8)	331.4 (66.0)	334.7 (66.7)
LSM (SE) change from baseline 8 hours postdose	-7.4 (7.8)	0.8 (7.6)	-1.2 (7.6)	-3.3 (7.7)
Speed of Memory Retrieval, msec				
4-hour baseline, mean (SD)	4633.6 (936.3)	4654.4 (927.9)	4622.2 (931.8)	4619.0 (940.4)
LSM (SE) change from baseline 4 hours postdose	-323.7 (96.7)	259.1 (97.4)*	-128.0 (100.4)[‡]	-23.5 (96.2) [§,‡]

8-hour baseline, mean (SD)	4615.2 (900.8)	4618.8 (896.4)	4620.2 (903.4)	4605.0 (911.0)
LSM (SE) change from baseline 8 hours postdose	-235.1 (97.5)	-132.6 (96.2)	-309.7 (97.3)	-249.0 (96.5)

*$p \leq 0.0001$ vs PBO, $^{\dagger}p < 0.05$ vs ZOL, $^{\ddagger}p < 0.01$ vs ZOL, $^{\S}p < 0.01$ vs PBO.

p values based on mixed-effect model repeated measurement analysis with treatment, sequence, period, baseline (time-matched), time (h postdose), treatment × time, and baseline × time as fixed effects, and time with subject as a random effect and a repeated effect for time, with subject within sequence. Only subjects with complete data were included in this analysis.

Power of Attention: lower values reflect better performance; higher values reflect impairment.

Continuity of Attention: higher values reflect better performance; lower values reflect impairment.

Quality of Memory: higher values reflect better performance; lower values reflect impairment.

Speed of Memory Retrieval: lower values reflect better performance; higher values reflect impairment.

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, LSM = least squares mean, MNAR = missing not at random, PBO = placebo, SD = standard deviation, SE = standard error, ZOL = zolpidem extended release 6.25 mg.

Figure S1—Flow of subjects through the trial.

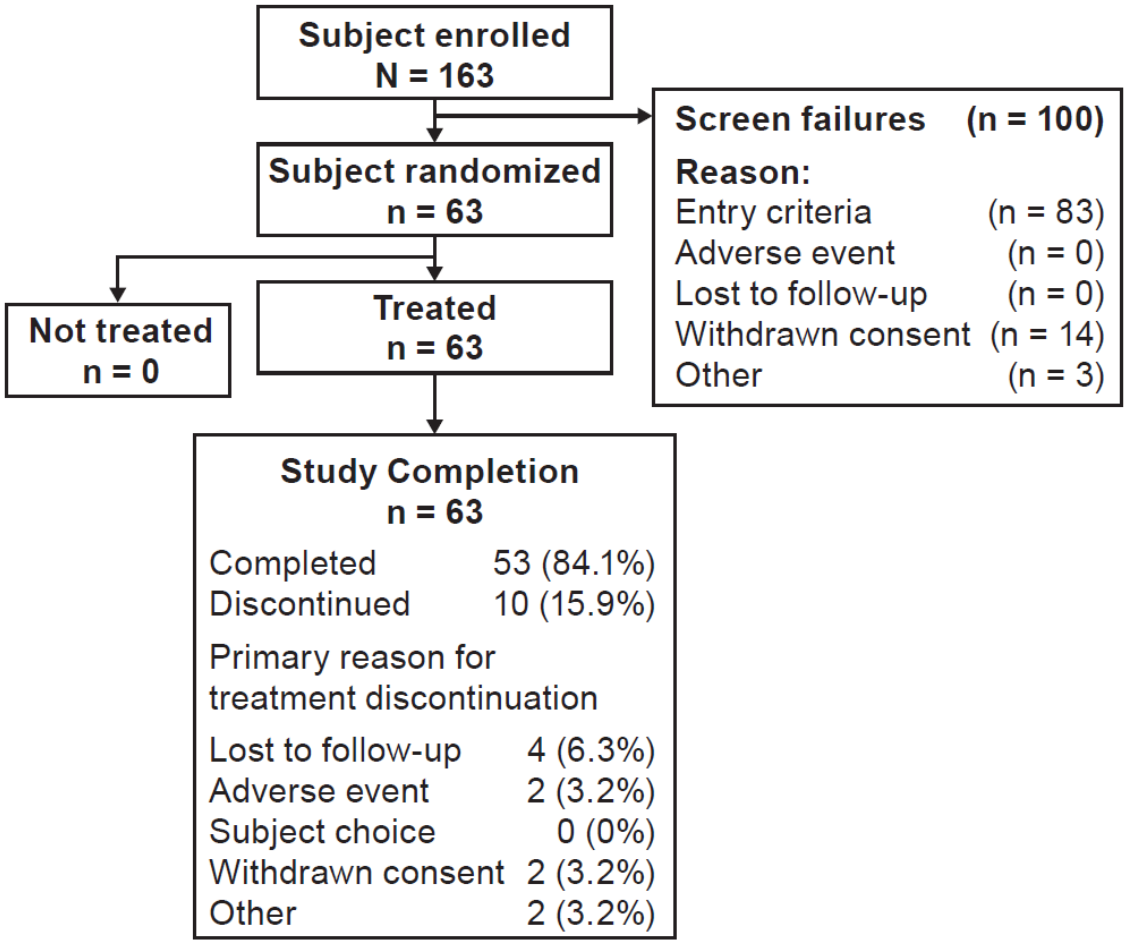
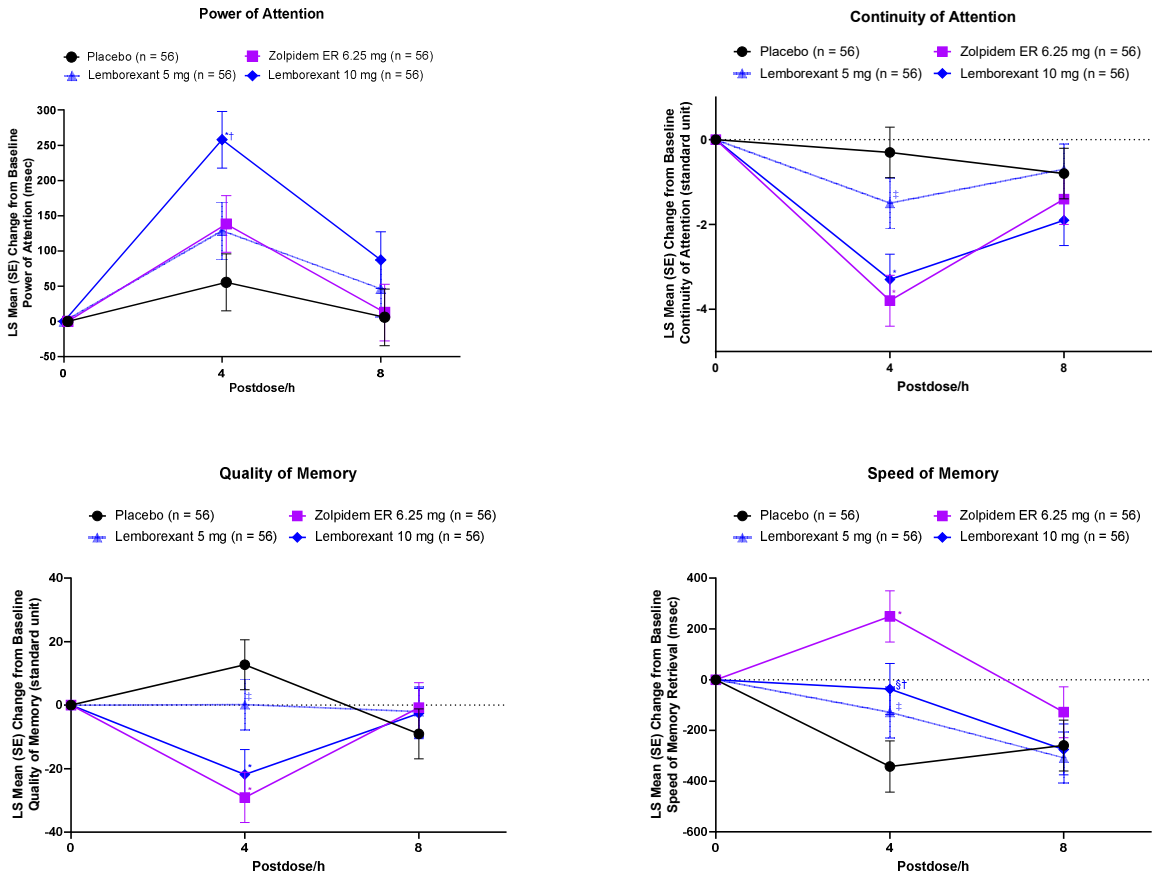


Figure S2—Change from baseline for cognitive performance assessment battery domains.



*p ≤ 0.0001 vs PBO, †p < 0.05 vs ZOL, ‡p < 0.01 vs ZOL, §p < 0.01 vs PBO

p values based on mixed-effect model repeated measurement analysis with treatment, sequence, period, baseline (time-matched), time (h postdose), treatment × time, and baseline × time as fixed effects, and time with subject as a random effect and a repeated effect for time, with subject within sequence. Only subjects with complete data were included in this analysis.

Power of Attention: lower values reflect better performance; higher values reflect impairment.

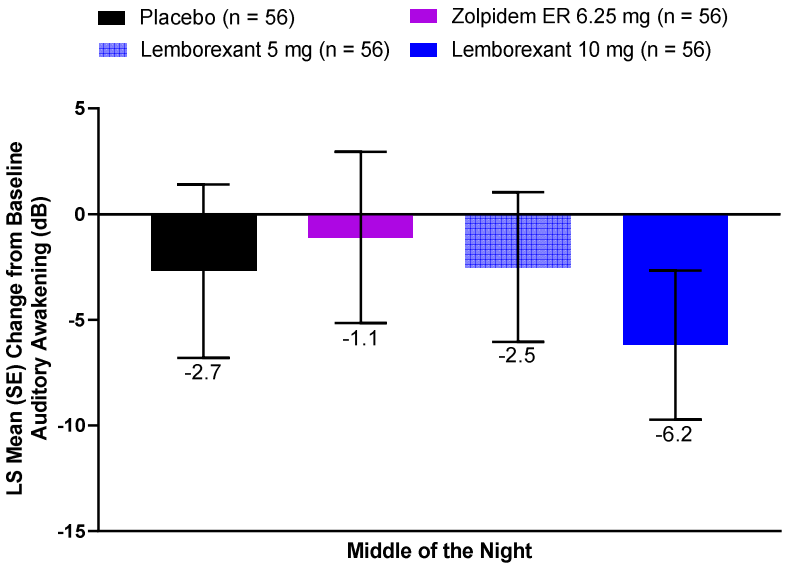
Continuity of Attention: higher values reflect better performance; lower values reflect impairment.

Quality of Memory: higher values reflect better performance; lower values reflect impairment.

Speed of Memory Retrieval: lower values reflect better performance; higher values reflect impairment.

ER = extended release, LS = least squares, SE = standard error.

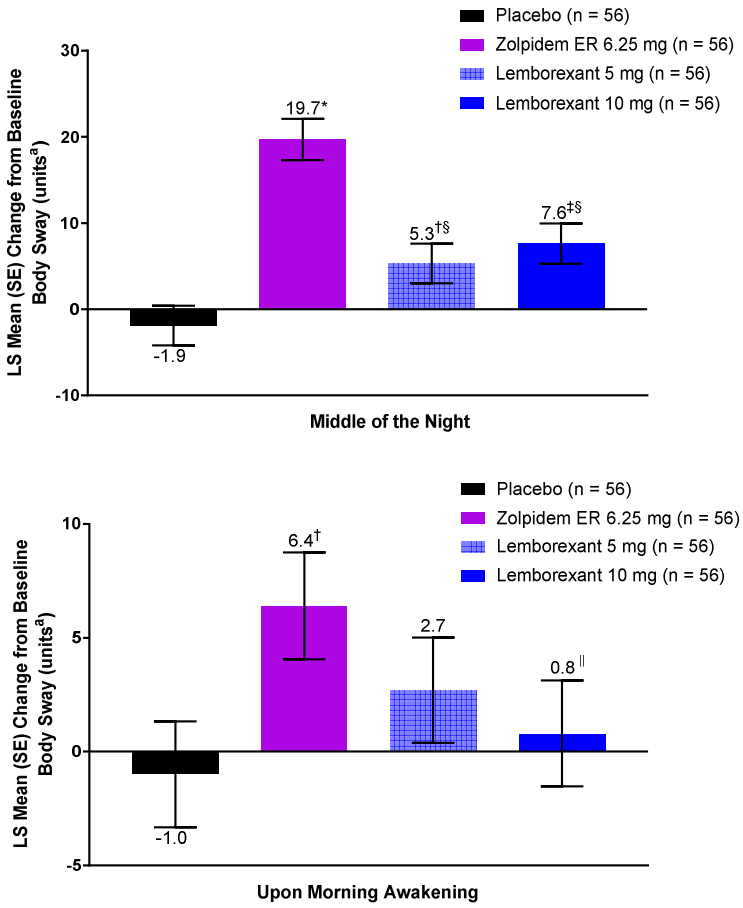
Figure S3—Change from baseline auditory awakening threshold (MNAR analysis).



There were no statistically significant differences in change from baseline in auditory awakening threshold between lemborexant and zolpidem vs placebo or lemborexant vs zolpidem.

dB = decibel, ER = extended release, LS = least squares, MNAR = missing not at random, SE = standard error.

Figure S4—Change from baseline body sway in (A) the middle of the night and (B) upon morning awakening (MNAR analysis).



*p ≤ 0.0001, †p < 0.05, ‡p ≤ 0.001 vs PBO; §p ≤ 0.0001, ‖ p < 0.05 vs ZOL based on mixed-effect model repeated measurement analysis with treatment, sequence, period, baseline (time-matched), time (h postdose), treatment × time, and baseline × time as fixed effects, and time with subject as a random effect and a repeated effect for time, with subject within sequence.

[a]A unit of body sway is defined as 1/3 degree angle of arc movement of the ataxiameter.

ER = extended release, LS = least squares, MNAR = missing not at random, SE = standard error.

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