Response to Treatment With Lemborexant: Subjects With Irregular Sleep-Wake Rhythm Disorder and Alzheimer's Disease Dementia

P2-617

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Introduction

- Irregular sleep-wake rhythm disorder (ISWRD) is a circadian rhythm sleep disorder, distinct from insomnia, which is characterized by the irregular distribution of sleep bouts across the 24-hour period rather than consolidated sleep at night.[1]
- ISWRD symptoms are common in patients with Alzheimer's disease dementia (AD-D).[2,3]
- Pathology of ISWRD includes disturbed circadian rhythmicity,[1] neuronal loss in the suprachiasmatic nuclei and pineal gland,[4] and decreased amplitude of other circadian rhythms such as melatonin and body temperature.
- Additionally, recent evidence suggests ISWRD may be due to a dysfunctional orexin system.[5]
- No adequate pharmacologic or nonpharmacologic treatment for ISWRD is currently available.
- Lemborexant (LEM) is a dual orexin receptor antagonist in development for the treatment of insomnia and ISWRD.[6]
- In 2 phase 3 studies for insomnia (SUNRISE-1 [NCT02783729; E2006-G000-304] and SUNRISE-2 [NCT02952820; E2006-G000-303]), LEM demonstrated greater improvements in subject-reported sleep onset and sleep maintenance outcomes vs placebo (PBO) for 1 month and 6 months, respectively. LEM also showed greater improvements in objective measures of sleep onset and sleep maintenance vs zolpidem tartrate extended release over 1 month in SUNRISE-1. In both studies, LEM was well tolerated.[7,8]
- This phase 2 proof-of-concept study evaluated the effects of LEM vs PBO on circadian, nighttime, and daytime endpoints in subjects with ISWRD and AD-D.

Methods

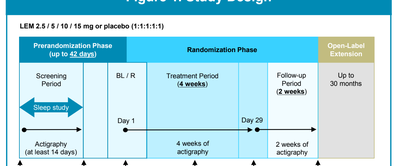
Participants

- Men and women 60-90 years of age.
- Documentation of diagnosis with AD-D on the basis of the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines.[9]
- Mini-Mental State Exam (MMSE) score 10-26.
- Met *Diagnostic and Statistical Manual of Mental Disorders* – 5th Edition criteria for circadian rhythm sleep disorder, irregular sleep-wake type.[10]
- Frequency of complaint of sleep and wake fragmentation ≥ 3 days per week for ≥ 3 months.
- Mean sleep efficiency measured by actigraphy < 87.5% in the nocturnal sleep period and mean wake efficiency (aWE) < 87.5% during the wake period.
- Confirmation by actigraphy of a combination of sleep bouts of > 10 minutes during the wake period plus wake bouts of > 10 minutes during the sleep period, totaling at least 4 bouts per 24-hour period, ≥ 3 days per week.
- No more than mild sleep apnea.
- Able to tolerate wearing an actigraph.

Study Design

- This phase 2 study (NCT03001557; E2006-G000-202) was a randomized, double-blind, multicenter, global, PBO-controlled, parallel-group trial comprising 3 phases: Prerandomization, Randomization (Core), and Open-Label Extension (Figure 1). The Open-Label Extension is ongoing.

Figure 1. Study Design



Visit 1 = Screening; Visit 2 = caregiver visit, download actigraphy data; Visit 3 = confirm eligibility and dispense study drug; Visit 4 = subject and caregiver visit, download actigraphy data and perform safety assessments; Visit 5 = end of treatment assessments, download actigraphy data; Visit 6 = end-of-study assessments, download actigraphy data.
BL, baseline; LEM, lemborexant; R, randomization.

- During Screening and the Randomization phases, subjects wore an actigraph (MotionWatch 8, CamNtech, Boerne, TX) continuously on the nondominant wrist for at least 14 days to qualify and for 28 days during PBO or LEM treatment.
- During the Core phase, subjects were randomized to PBO or LEM (2.5 mg [LEM2.5], 5 mg [LEM5], 10 mg [LEM10], or 15 mg [LEM15]) for 4 weeks.
- Actigraphy data were collected in 30-second epochs and scored using an algorithm as sleep or wake.
- Actigraphy data analysis was informed by a sleep diary completed daily by caregivers.
- Analyses of circadian parameters included:
  - Relative amplitude (RA), which standardizes for activity-level differences across subjects and reflects the strength of the circadian signal and differentiation between daytime and nighttime activity levels.
  - Least active 5 hours of the day (L5), defined as the average activity across the least active 5-hour period of the 24-hour rest-activity rhythm; higher values indicate restlessness.
  - Most active 10 hours of the day (M10), defined as the average activity across the most active 10-hour period of 24-hour rest-activity rhythm; higher values indicate more activity.
- Daytime wake endpoints included:
  - Average duration of sleep bouts, defined as consolidated naps that were ≥ 10 minutes in duration.
  - Wake Fragmentation Index (WFI), defined as the sum of an immobility index (II) and a fragmentation index (FI), with II = (epochs of immobility per the 16 hours outside of the defined sleep period) × 100 and FI = (number of ≤ 1-minute periods of mobility/total number of periods of mobility in the 16 hours outside of the defined sleep period) × 100.
- Nighttime sleep-related endpoints included:
  - Sleep Fragmentation Index (SFI), which represents transitions between sleep and wake throughout night; higher value indicates fragmented sleep.
    - SFI was calculated as the sum of a movement index (MI) and an FI, with MI = (epochs of wake per time in bed) × 100 and FI = (number of ≤ 1-minute periods of immobility/total number of periods of immobility of all durations during the defined nocturnal sleep period) × 100.
  - Total sleep time (TST), defined as minutes of sleep during the night.
- The MMSE[11] and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[12] were administered prior to and at the end of treatment to assess for change in cognitive function.

Statistical Analysis

- Efficacy analyses were performed on the Full Analysis Set, defined as the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 post-dose efficacy measurement, unless otherwise specified.
- To identify relevant efficacy variables, a Gaussian graphical model was used. Regularization method was applied to infer a sparse network topology of interconnectedness among the efficacy variables.
- For all actigraphy parameters, baseline was defined as the average value of the last 7 days of Screening. For L5, M10, amplitude of the rest-activity rhythm, RA, interdaily stability (IS), and intradaily variability parameters, the weekly averages were calculated by actigraphy vendor.
- For these variables, the last record of Screening Period was considered as the baseline (the average of the last 7 days) of the Screening Period.
- Change from baseline in RA, L5, SFI, TST, and duration of daytime sleep bouts was analyzed using mixed-effect model for repeated measurement (MMRM) analysis, which included all data and was adjusted for the corresponding baseline value, country, treatment, time (Weeks 1, 2, 3, and 4), and the interaction of treatment by time.
- The MMRM model accounted for any missing data and assumed that missing data were missing at random.
- 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 post-dose safety assessment.
- Responders were defined separately as:
  - Subjects whose mean activity level dropped from baseline at Week 4 during L5 (sleep) and whose mean duration of sleep bouts during the wake period dropped from baseline at Week 4. A nominal threshold of 5% (rather than 0) was applied for the definition.
  - Subjects whose mean duration of sleep bouts during the wake period dropped from baseline at Week 4, whose mean RA of sleep-wake cycle improved from baseline at Week 4, and whose mean IS of sleep-wake cycle improved.
- For responder analyses, the percentage change from baseline was used as the metric for change for each variable.

Results

- 168 subjects were screened, 62 were randomized, and 62 completed the Core study.
- Fifty subjects who were randomized to LEM (12, 13, 13, and 12 subjects in the LEM2.5, LEM5, LEM10, and LEM15 groups, respectively) and 12 subjects who were randomized to PBO received at least 1 dose of study drug.
- Baseline characteristics were balanced across the treatment groups (Table 1).

Table 1. Demographic and Baseline Characteristics

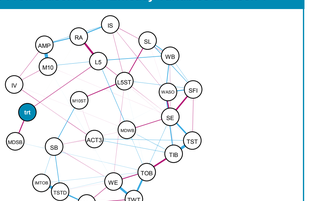
	Placebo (n = 12)	LEM2.5 (n = 12)	LEM5 (n = 13)	LEM10 (n = 13)	LEM15 (n = 12)
Age, y					
Mean (SD)	75.3 (6.2)	76.5 (6.3)	76.9 (8.0)	71.8 (7.1)	71.9 (6.1)
≥ 60–< 65	0	0	1 (7.7)	1 (7.7)	2 (16.7)
≥ 65–< 75	4 (33.3)	4 (33.3)	4 (30.8)	9 (69.2)	4 (33.3)
≥ 75–< 85	8 (66.7)	7 (58.3)	7 (53.8)	2 (15.4)	6 (50.0)
≥ 85–< 90	0	1 (8.3)	1 (7.7)	1 (7.7)	0
Sex, n (%)					
Male	5 (41.7)	6 (50.0)	5 (38.5)	7 (53.8)	2 (16.7)
Female	7 (58.3)	6 (50.0)	8 (61.5)	6 (46.2)	10 (83.3)
Race, n (%)					
White	8 (66.7)	9 (75.0)	8 (61.5)	9 (69.2)	9 (75.0)
Black	2 (16.7)	1 (8.3)	2 (15.4)	1 (7.7)	1 (8.3)
Japanese	2 (16.7)	2 (16.7)	2 (15.4)	3 (23.1)	2 (16.7)
Other	0	0	1 (7.7)	0	0
BMI, mean (SD), kg/m²	29.3 (6.2)	26.1 (4.2)	24.7 (3.8)	26.3 (5.7)	30.5 (11.6)

BMI, body mass index; LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; SD, standard deviation.

Network Analysis of Efficacy Variables

- As efficacy variables are interrelated, an advanced network analysis was performed to elucidate the relational structure of circadian rhythm variables and treatment (Figure 2).
- The main efficacy variables identified from the network analysis were mean duration of sleep bouts during the wake period, and activity level during the L5, RA, and IS of the sleep-wake cycle.

Figure 2. Partial Correlation Network Analysis of Percentage Change From Baseline for Efficacy Variables at Week 4



The presence of a line indicates existence of a partial correlation between the variables. A blue line represents a positive correlation and a pink line represents an inverse correlation. Line thickness represents the strength of the correlation between the variables.
ACT3, average activity in first 3-hour morning logged time; AMP, average amplitude; HH, hours on 24-hour clock; IMTOB, average immobile minutes out of bed logged time (min); IS, average interdaily stability; IV, average intradaily variability; L5, average least active 5-hour period per 24-hour period; LSST, average start hour of L5 (HH); M10, average most active 10-hour period per 24-hour period; M10ST, average start hour of M10 (HH); MDWB, mean duration of sleep bouts logged time (min); MDWB, mean duration of wake bouts logged time (min); RA, average relative amplitude; SB, average number of sleep bouts logged time; SE, average sleep efficiency logged time (%); SFI, average Sleep Fragmentation Index logged time (%); SL, average sleep latency (min); TIB, average time in bed logged time (min); TOB, average time out of bed logged time (min); trt, treatment; TST, average total sleep time logged time (min); TSTD, average total sleep time day (min); TWT, average total wake time logged time (min); WASO, average wake after sleep onset logged time (min); WB, average number of wake bouts logged time; WE, average wake efficiency logged time (%); WFI, average Wake Fragmentation Index logged time (%).

Circadian Endpoints

- Compared with baseline values, LEM5 and LEM15 led to a significantly higher RA vs PBO ($P < 0.05$) across 4 weeks of treatment (Table 2).
  - Higher amplitude means more distinction between night and day.
  - Consistent improvement in RA was observed across 4 weeks of treatment for LEM5 compared with PBO (Figure 4A).
- L5 significantly decreased vs PBO at doses of LEM2.5, LEM5, and LEM15, indicating a more quiet and restful nighttime sleep (Table 2).
  - Consistent improvements in L5 were observed across 4 weeks of treatment.

Daytime Wake Endpoints

- Across 4 weeks of treatment, sleep bouts during the day were numerically shorter with LEM5, LEM10, and LEM15 vs PBO (Table 2; Figure 3).
  - LEM5 appeared to be the most effective dose in the study.
  - Mean duration of sleep bouts during the day were numerically shorter with LEM5 vs PBO at each week of the study (Figure 4B).
- Numeric decreases in WFI were observed with LEM5 compared with PBO after 1, 3, and 4 weeks of treatment (Figure 4C).
- Average TST during daytime decreased with LEM5 after 3 and 4 weeks of treatment (Figure 4D).

Nighttime Sleep-Related Endpoints

- Numeric improvements in SFI were observed vs PBO across all 4 weeks of treatment with LEM2.5, LEM5, and LEM15, indicating more consolidated, thus less fragmented, sleep (Table 2).
- Numeric improvements in TST during the night were observed vs PBO across all 4 weeks of treatment with LEM5 and LEM15 (Table 2).

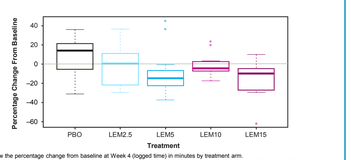
Responder Analysis

- A greater percentage of subjects in each LEM group, compared with PBO, met responder criteria defined as > 5% decreases from baseline at 4 weeks for both L5 and mean duration of sleep bouts during wake (Figure 5A).
- Additionally, a greater percentage of subjects in each LEM group, compared with PBO, met the more restrictive responder criteria when defined as changes from baseline at 4 weeks of > 0% for mean RA and IS, and < 0% for mean duration of sleep bouts during wake (Figure 5B).

Safety

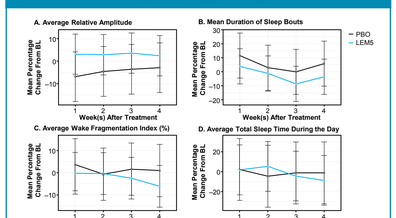
- Treatment-emergent adverse events (TEAEs) were observed in all treatment groups including PBO (Table 3).
  - All but 2 TEAEs were mild in severity.
- No deaths, serious adverse events, or discontinuations for any reason were reported.
- TEAEs observed were consistent with those seen in the insomnia program.
- No falls or confusion were reported.
- No significant worsening of cognition was observed (MMSE, ADAS-Cog) (Table 4).

Figure 3. Boxplots of Percentage Change From Baseline by Treatment in Mean Duration of Sleep Bouts During Wake Periods at Week 4



Boxplots show the percentage change from baseline at Week 4 (logged time) in minutes by treatment arm.
LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; PBO, placebo.

Figure 4. Longitudinal Plots of Efficacy Variables Over 4 Weeks of Treatment for LEM5 vs PBO



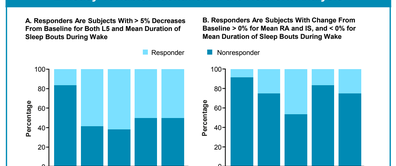
Mean (95% confidence interval) percentage change from baseline at each week after treatment was determined using mixed-effect model for repeated measurement analysis.
BL, baseline; LEM5, lemborexant 5 mg; PBO, placebo.

Table 2. Circadian, Daytime, and Nighttime Outcomes at Baseline and Change From Baseline at Week 4

	PBO (n = 12)	LEM2.5 (n = 12)	LEM5 (n = 13)	LEM10 (n = 13)	LEM15 (n = 12)
Circadian outcomes					
Least active 5 hours, mean (SD), activity counts					
Baseline	1163.5 (373.3)	1266.4 (678.1)	1163.2 (591.8)	1257.1 (836.6)	1490.4 (963.1)
Week 4	1493.4 (750.6)	1017.0 (603.5)	997.8 (621.6)	1463.6 (827.9)	1272.4 (907.3)
Change from baseline at Week 4	293.1 (662.6)	−334.0 (476.4)	−344.5 (419.1)	30.5 (772.5)	−160.7 (471.3)
LS mean difference vs PBO (95% CI)		−389.9 (−739.2 to −40.6)	−403.0 (−751.7 to −54.3)	−141.0 (−489.9 to 207.8)	−367.8 (−717.9 to −17.8)
Relative amplitude of the rest-activity rhythm, mean (SD)					
Baseline	0.73 (0.14)	0.79 (0.14)	0.82 (0.09)	0.77 (0.17)	0.76 (0.15)
Week 4	0.73 (0.14)	0.78 (0.15)	0.83 (0.10)	0.72 (0.13)	0.79 (0.17)
Change from baseline at Week 4	0.00 (0.12)	0.01 (0.06)	0.05 (0.05)	0.01 (0.14)	0.02 (0.07)
LS mean difference vs PBO (95% CI)		0.02 (−0.03 to 0.07)	0.06 (0.01-0.12)	0.00 (−0.05 to 0.06)	0.06 (0.00-0.11)
Daytime outcomes					
Duration of sleep bouts,[a] mean (SD)					
Baseline	18.36 (4.62)	20.65 (3.64)	23.13 (5.92)	19.84 (3.36)	23.30 (10.86)
Week 4	19.38 (5.71)	19.50 (5.50)	20.37 (4.55)	19.59 (3.11)	18.00 (2.88)
Change from baseline	1.00 (4.57)	−1.31 (3.64)	−2.80 (5.73)	−0.03 (2.31)	−5.30 (9.75)
LS mean difference vs PBO (95% CI)		0.06 (−2.45 to 2.58)	−0.24 (−2.82 to 2.34)	−0.29 (−2.75 to 2.16)	−1.56 (−4.11 to 1.00)
Wake Fragmentation Index,[a] mean (SD)					
Baseline	92.43 (18.55)	85.72 (16.14)	86.53 (18.71)	94.76 (17.26)	87.96 (15.93)
Week 4	90.67 (15.27)	89.44 (16.03)	78.74 (18.18)	100.08 (16.43)	89.18 (16.12)
Change from baseline	−3.01 (10.62)	4.55 (10.93)	−6.93 (14.43)	2.77 (13.41)	1.22 (8.05)
LS mean difference vs PBO (95% CI)		4.85 (−2.62 to 12.31)	−3.87 (−11.26 to 3.52)	6.78 (−0.47 to 14.03)	3.02 (−4.34 to 10.38)
Nighttime outcomes					
Sleep Fragmentation Index,[a] mean (SD)					
Baseline	58.51 (12.92)	53.87 (17.59)	50.07 (12.49)	54.75 (16.38)	54.78 (15.34)
Week 4	59.15 (14.82)	50.45 (14.68)	48.78 (14.74)	57.61 (20.06)	53.10 (18.55)
Change from baseline at Week 4	−1.39 (19.38)	−1.35 (8.82)	−1.96 (8.46)	−0.45 (13.39)	−1.68 (12.68)
LS mean difference vs PBO (95% CI)		−5.10 (−12.24 to 2.05)	−6.11 (−13.33 to 1.12)	0.680 (−6.26 to 7.62)	−3.14 (−10.18 to 3.90)
Total sleep time during the night,[a] mean (SD), min					
Baseline	413.74 (79.21)	415.49 (116.93)	408.71 (88.96)	413.33 (76.36)	399.13 (59.33)
Week 4	421.76 (57.18)	395.56 (67.27)	419.26 (83.45)	412.75 (89.53)	412.50 (64.24)
Change from baseline at Week 4	3.94 (79.12)	2.29 (42.16)	7.59 (70.60)	0.81 (35.70)	13.38 (34.68)
LS mean difference vs PBO (95% CI)		−0.59 (−32.92 to 31.74)	10.73 (−21.41 to 42.86)	−1.25 (−32.86 to 30.35)	16.46 (−15.65 to 48.57)

[a]Calculations based on the logged time in bed.
CI, confidence interval; LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; LS, least squares; PBO, placebo; SD, standard deviation.

Figure 5. Responder Analyses at 4 Weeks of Treatment for Main Efficacy Variables Identified in the Network Analysis



IS, interdaily stability; LS, least active 5 hours of the day; LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; PBO, placebo; RA, relative amplitude.

Table 3. Summary of TEAEs From Core Study

Category	PBO (n = 12)	LEM2.5 (n = 12)	LEM5 (n = 13)	LEM10 (n = 13)	LEM15 (n = 12)
Any TEAE, n	4	3	3	4	6
Severe TEAE, n	0	0	0	0	1
Serious adverse event, n	0	0	0	0	0
TEAE leading to discontinuation, n	0	0	0	0	0
TEAE preferred term,[a] n (%)					
Constipation	0	0	0	1 (7.7)	2 (16.7)
Somnolence	0	0	0	1 (7.7)	2 (16.7)
Arthralgia	0	0	0	0	2 (16.7)
Headache	0	0	0	0	2 (16.7)
Nightmare	0	0	0	2 (15.4)	0

[a]Includes TEAEs reported by more than 2 subjects in any active treatment group.
LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; PBO, placebo; TEAE, treatment-emergent adverse event.

Table 4. Cognitive Assessments at Baseline and Day 29

	PBO (n = 12)	LEM2.5 (n = 12)	LEM5 (n = 13)	LEM10 (n = 13)	LEM15 (n = 12)
MMSE total score, mean (SD)					
Baseline	19.8 (5.0)	22.2 (4.2)	22.1 (2.8)	19.8 (4.4)	21.0 (4.2)
Day 29	21.1 (6.2)	23.5 (5.0)	22.6 (2.7)	20.3 (4.6)	20.1 (5.8)
Change from baseline	1.3 (2.5)	1.3 (2.1)	0.5 (1.9)	0.5 (3.1)	−0.9 (3.7)
LS mean difference vs PBO (95% CI)		0.1 (−2.3 to 2.4)	−0.9 (−3.2 to 1.5)	−0.7 (−3.0 to 1.5)	−2.1 (−4.4 to 0.1)
P value[a]		0.9446	0.4590	0.5112	0.0636
ADAS-Cog score, mean (SD)					
Baseline	29.4 (17.4)	29.9 (11.7)	27.0 (8.8)	30.7 (15.5)	28.9 (14.5)
Day 29	30.3 (18.5)	26.2 (12.6)	28.0 (9.9)	29.7 (12.4)	28.8 (13.9)
Change from baseline	0.8 (3.8)	−3.7 (5.0)	1.0 (3.9)	−1.0 (5.4)	2.6 (4.5)
LS mean difference vs PBO (95% CI)		−4.5 (−8.3 to −0.7)	0.3 (−3.5 to 4.2)	−1.6 (−5.3 to 2.1)	1.5 (−2.4 to 5.5)
P value[a]		0.0227	0.8592	0.3900	0.4454

[a]Based on an analysis of covariance model adjusted for baseline value and country.
ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI, confidence interval; LEM2.5, lemborexant 2.5 mg; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; LEM15, lemborexant 15 mg; LS, least squares; MMSE, Mini-Mental State Examination; PBO, placebo; SD, standard deviation.

Conclusions

- This pilot study provides preliminary evidence that LEM improved both 24-hour circadian rhythm variables and nocturnal sleep variables in subjects with ISWRD and AD-D.
- LEM decreased mean duration of sleep bouts during the daytime and decreased L5, supporting consolidation of sleep at night.
  - These results are important because ISWRD is a circadian rhythm sleep disorder, and fragmented nighttime sleep in ISWRD is a major problem for patient safety and contributes to increased caregiver burden.
- LEM exhibited treatment benefit as detected by the interconnected efficacy variables in ISWRD patients on their circadian rhythm.
- LEM was well tolerated in subjects with ISWRD and AD-D.

References

1. Zee PC, Vitiello MV. *Sleep Med Clin.* 2009;4:213-218. **2.** Brzezka A, et al. *Front Neurosci.* 2018;12:330. **3.** Musiek ES, et al. *Exp Mol Med.* 2015;47:e148. **4.** Zhu L, Zee PC. *Neurol Clin.* 2012;30:1167-1191. **5.** Liguori C, et al. *Neurobiol Aging.* 2016;40:120-126. **6.** Murphy P, et al. *J Clin Sleep Med.* 2017;13:1289-1299. **7.** Rosenberg R, et al. Comparison of lemborexant with zolpidem tartrate extended release and placebo: topline results from a phase 3 study in subjects 55 years and older with insomnia (SUNRISE-1). Poster presented at: 24th Congress of the European Sleep Research Society; September 25-28, 2018; Basel, Switzerland. **8.** Yardley J, et al. Efficacy of lemborexant compared with placebo in adult and elderly subjects with insomnia: results from a phase 3 study (SUNRISE-2). Poster presented at: Advances in Sleep and Circadian Science/Sleep Research Society 2019; February 1-4, 2019; Clearwater Beach, FL. **9.** McKhann GM, et al. *Alzheimers Dement.* 2011;7:263-269. **10.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition. https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596. Published 2013. Accessed January 7, 2019. **11.** Folstein MF, et al. *J Psychiatr Res.* 1975;12:189-198. **12.** Rosen WG, et al. *Am J Psychiatry.* 1984;141:1356-1364.

Disclosures

- ST is an employee of Pacific Research Network.
- MB, NR, GF, and MM are employees of Eisai Inc. NK is an employee of Eisai Co. Ltd.
- MK is an employee of The Siesta Group, the central actigraphy scoring vendor.

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