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Lemborexant Effect on Sleep Parameters in Adults With Moderate or Severe Chronic Obstructive Pulmonary Disease

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Introduction

- Patients with chronic obstructive pulmonary disease (COPD) commonly experience sleep disruption, including negative effects on sleep initiation, architecture, and maintenance[1-3]
- Some commonly prescribed hypnotics impact respiratory function (eg, benzodiazepines); therefore, when new hypnotics are under development, it is important to assess the potential impact on respiratory variables in a vulnerable patient population such as those with COPD[1]
- Lemborexant (LEM) is a competitive dual orexin-receptor antagonist (DORA) approved in the United States, Japan, Canada, Australia, and several Asian and Middle Eastern countries to treat adults with insomnia[4-7]
  - In two phase 3 studies, LEM significantly improved sleep onset and sleep maintenance compared with placebo (PBO) in participants with insomnia[6,7]
- Study E2006-A001-113 (Study 113; NCT04647383) was a phase 1 clinical trial that investigated the respiratory safety of LEM in adult participants with untreated moderate-to-severe COPD
  - Study 113 is the first DORA safety study to include participants with severe COPD
- In Study 113, there were no adverse impacts on peripheral oxygen saturation and the apnea-hypopnea index (AHI) during total sleep time (TST) on Day 1 or Day 8 of daily LEM 10 mg (LEM10) treatment compared with PBO, demonstrating respiratory safety with single and multiple dosing[8]
- Since patients with COPD report sleep disruptions irrespective of the presence of insomnia, and sleep disturbance is associated with reduced quality of life in these patients,[1] it was of interest to analyze the impact of LEM on sleep variables in participants with COPD

Objective

- This post hoc analysis aimed to assess the impact of LEM10 treatment on sleep variables in participants with moderate-to-severe COPD

Methods

Study Design

- Study 113 was a multicenter, multiple-dose, randomized, double-blind, PBO-controlled, 2-period crossover study (Figure 1)

Participants

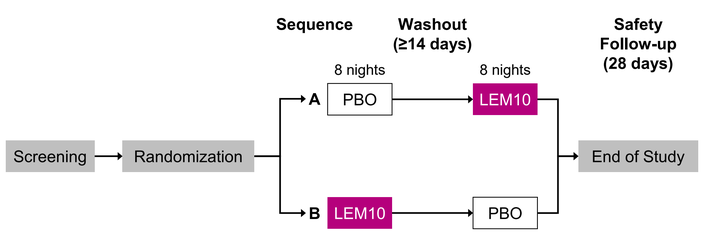
Key Inclusion Criteria

- Adults ≥45 to ≤90 years of age
- Regularly reporting ≥5.5 h of sleep/night, with normal bedtime between 9:00 PM and 12:00 AM
- Body mass index <40 kg/m^2
- AHI <15 on polysomnography (PSG) screening
- SpO_2 ≥94% by pulse oximeter at screening *plus* the following:
  - SpO_2 >90% during awake time
  - SpO_2 during sleep ≥80% for at least 75% of the recording period, with no more than 5 continuous min <80% and with no SpO_2 readings <70%
- Forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio <0.70 *plus* 1 of the following:
  - 50% ≥ FEV1 < 80% predicted (GOLD 2, moderate COPD)
  - 30% ≥ FEV1 < 50% predicted (GOLD 3, severe COPD)

Key Exclusion Criteria

- Continuous positive airway pressure (CPAP) device usage
- Use of oxygen therapy continuously (>16 h/day) or during PSG
- Recent changes to COPD medications or recent acute exacerbation of COPD within 3 months of enrollment
- Diagnosis of a significant medical or psychiatric illness
- Evidence of an active respiratory disorder, or diagnosis or symptoms of restless legs syndrome, periodic limb movement disorder, circadian rhythm sleep disorder, narcolepsy, or parasomnia
  - Insomnia was not specifically excluded unless participants habitually slept <5.5 h/night

Figure 1. Study Design



Note: On Days 1 and 8 of each treatment period, the study drug was administered in the clinic 5 min before lights out. On Days 2-7 during each treatment period, participants were instructed to take the study drug at home within 5 min of bedtime.
LEM10, lemborexant 10 mg; PBO, placebo.

Outcomes

Efficacy Assessments

- PSG was performed on Day 1 (after a single bedtime dose) and Day 8 (after multiple bedtime doses) during both treatment periods to assess:
  - Latency to persistent sleep (LPS)
  - Sleep efficiency
  - Wake after sleep onset (WASO)
  - TST
- The PSG recording began at lights off and continued for 8 h; records were scored centrally in 30-s epochs by trained PSG scorers according to standard criteria

Safety

- Safety assessments included monitoring of treatment-emergent adverse events, clinical laboratory evaluations, vital signs, weight, electrocardiograms, suicidality, and physical examinations

Statistical Analyses

- The Safety Analysis Set included all participants who received ≥1 dose of study drug and had ≥1 post-dose safety assessment
- The Pharmacodynamic (PD) Analysis Set included all participants who received ≥1 dose of study drug in each treatment period and who had sufficient PD data to derive ≥1 primary PD parameter
- PSG sleep parameters were analyzed on Days 1 and 8 of treatment using a mixed-effects model with fixed effects for sequence, period, and treatment and a random effect for participant
  - Sleep parameters were summarized as least squares mean (LSM) estimates with LSM differences (LEM – PBO) and associated standard error

Results

- Most participants were ≥65 years old (76.7%) and female (70%) (Table 1)
- 25 (83.3%) participants had moderate COPD, and 5 (16.7%) had severe COPD
- Six (20%) participants had a medical history of insomnia

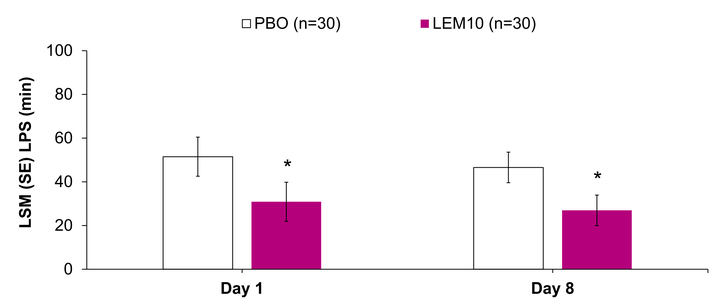
Table 1. Demographic and Baseline Characteristics (Safety Analysis Set)

	Sequence A (n=14)	Sequence B (n=16)	Overall (N=30)
Age, y[a]			
Mean (SD)	69.4 (6.2)	69.0 (6.5)	69.2 (6.3)
Median (range)	67.5 (62-80)	70.5 (58-80)	69.0 (58-80)
≥65 y, n (%)	11 (78.6)	12 (75.0)	23 (76.7)
Sex, n (%)			
Male	3 (21.4)	6 (37.5)	9 (30.0)
Female	11 (78.6)	10 (62.5)	21 (70.0)
Race, n (%)			
White	13 (92.9)	14 (87.5)	27 (90.0)
Black or African American	1 (7.1)	2 (12.5)	3 (10.0)
Asian	0	0	0
Other	0	0	0
BMI, mean (SD), kg/m^2	29.5 (6.4)	28.6 (5.0)	29.0 (5.6)
SpO_2 during TST, mean (SD), %	91.6 (2.5)	91.7 (2.4)	91.6 (2.4)
AHI during TST, mean (SD), events/h	4.5 (3.4)	4.7 (3.7)	4.6 (3.5)

[a]Age was calculated at the date of informed consent.
AHI, apnea-hypopnea index; BMI, body mass index; SD, standard deviation; SpO_2, peripheral oxygen saturation; TST, total sleep time.

- Following a single dose (Day 1) and multiple doses (Day 8) of study drug, LPS was significantly shorter with LEM10 compared with PBO (P<0.05) (Figure 2)

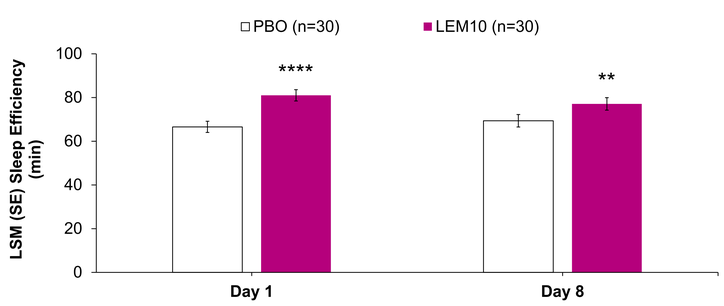
Figure 2. LPS



* P<0.05 vs PBO.
LEM10, lemborexant 10 mg; LPS, latency to persistent sleep; LSM, least squares mean; PBO, placebo; SE, standard error.

- Following a single dose (Day 1) and multiple doses (Day 8) of study drug, sleep efficiency was significantly higher with LEM10 compared with PBO (P<0.01) (Figure 3)

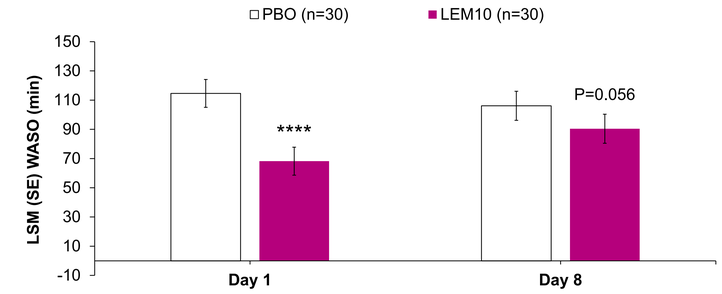
Figure 3. Sleep Efficiency



** P<0.01 vs PBO; **** P<0.0001 vs PBO.
LEM10, lemborexant 10 mg; LSM, least squares mean; PBO, placebo; SE, standard error.

- Following a single dose (Day 1) of study drug, WASO was significantly lower with LEM10 compared with PBO (P<0.0001) (Figure 4)

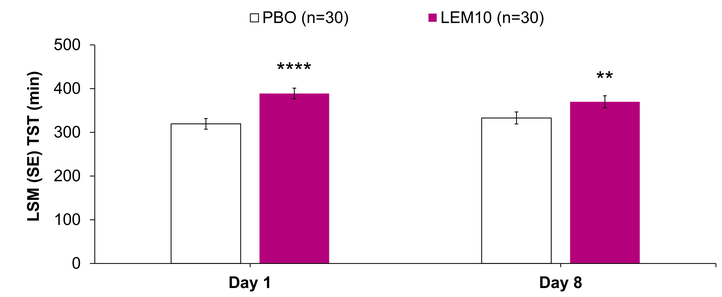
Figure 4. WASO



**** P<0.0001 vs PBO.
LEM10, lemborexant 10 mg; LSM, least squares mean; PBO, placebo; SE, standard error; WASO, wake after sleep onset.

- Following a single dose (Day 1) and multiple doses (Day 8) of study drug, TST was significantly longer with LEM10 compared with PBO (P<0.01) (Figure 5)

Figure 5. TST



** P<0.01 vs PBO; **** P<0.0001 vs PBO.
LEM10, lemborexant 10 mg; LSM, least squares mean; PBO, placebo; SE, standard error; TST, total sleep time.

- LEM was well tolerated, and adverse events reported were consistent with its known safety profile (Table 2)

Table 2. Safety Summary (Safety Population)

Category, n (%)	PBO (n=30)	LEM10 (n=30)
Any TEAE[a]	4 (13.3)	5 (16.7)
Treatment-related TEAE	1 (3.3)	2 (6.7)
Severe TEAE	0	1 (3.3)
Serious TEAE	0	1 (3.3)[b]
TEAE by ≥5% by Preferred Term, n (%)		
Headache	2 (6.7)	1 (3.3)

[a]TEAE is defined as an adverse event with onset date after the first dose of study drug up to 28 days after the last dose of study drug. For each row category, a participant with ≥2 adverse events in that category is counted only once.
[b]Participant sustained bone fractures that were judged to not be related to study treatment and did not lead to study withdrawal.
LEM10, lemborexant 10 mg; PBO, placebo; TEAE, treatment-emergent adverse event.

Conclusions

- When participants with untreated moderate-to-severe COPD, most of whom did not have a medical history of insomnia, were taking LEM10, sleep onset was shorter, sleep maintenance was better, and total sleep time was longer compared with when they were taking PBO
- LEM was well tolerated in patients with COPD, and there were no new safety signals in this patient population
- In combination with previous findings that demonstrated respiratory safety of LEM in patients with COPD,[8] these data suggest that LEM may be a potential treatment option for patients with COPD and insomnia

References

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Disclosures

GKZ: Employee and shareholder of Clinilabs Drug Development Corporation; has ownership interest in the Sleep Disorders Institute and Home Sleep and Respiratory Care; has served as a consultant for Eisai Inc., Janssen, Purdue, and Takeda; and has served on the speakers' bureau for Merck.
JYC, NH, and **MM:** Employees of Eisai Inc.

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