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Safety and Efficacy of Low-Sodium Oxybate in Participants With Narcolepsy With and Without Psychiatric Comorbidities: Subgroup Analysis of a Phase 3 Clinical Trial

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Introduction

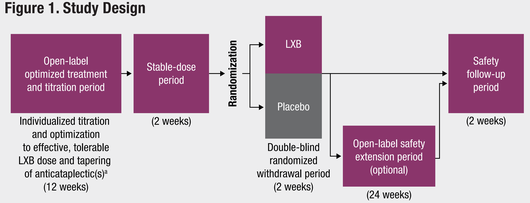
- Narcolepsy is a rare sleep disorder characterized by excessive daytime sleepiness, disrupted nocturnal sleep, cataplexy (in patients with narcolepsy type 1), and ancillary symptoms of sleep paralysis and hypnagogic and/or hypnopompic hallucinations[1]
- Narcolepsy and psychiatric comorbidities appear remarkably intertwined[2]
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration for treating cataplexy or excessive daytime sleepiness in patients ≥7 years of age with narcolepsy and for treating idiopathic hypersomnia in adults[3]
- Safety and efficacy of LXB in patients with narcolepsy with and without psychiatric comorbidities have not yet been assessed

Objective

- Assess the safety and efficacy of LXB in participants with narcolepsy with and without psychiatric comorbidities in a phase 3 clinical trial (NCT03030599)

Methods

Figure 1. Study Design



[a]Included selective serotonin-norepinephrine reuptake inhibitors/selective norepinephrine reuptake inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, pitolisant, and antidepressants with other mechanisms of action.
LXB, low-sodium oxybate.

- Eligible participants were 18–70 years of age with a diagnosis of narcolepsy with cataplexy based on criteria from the *International Classification of Sleep Disorders – Third Edition*[1] or the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[4]
- In this clinical trial, the primary efficacy endpoint was change in weekly number of cataplexy attacks from the end of the 2-week stable-dose period (SDP) to the end of the 2-week double-blind randomized withdrawal period (DBRWP)
- A key secondary endpoint was change in Epworth Sleepiness Scale (ESS) score from the end of the SDP to the end of the DBRWP
- Safety assessments included the Patient Health Questionnaire–9 (PHQ–9), the Columbia–Suicide Severity Rating Scale (C-SSRS), and treatment-emergent adverse events (TEAEs)

Results

Table 1. Concurrent and Past Psychiatric Comorbidities

Comorbidity	Total (N=50)[a]
Depression	26
Anxiety	22
Adjustment disorder with depressed mood	4
Attention-deficit/hyperactivity disorder	3
Somnambulism	3
Agoraphobia	1
Anxiety disorder	1
Autism spectrum disorder	1
Borderline personality disorder	1
Enuresis	1
Insomnia	1
Nightmare	1
Panic disorder	1
Persistent depressive disorder	1
Posttraumatic stress disorder	1
Rapid eye movement sleep behavior disorder	1
Sleep-related eating disorder	1

[a]Patients may have reported more than one comorbidity; therefore, the total may not sum to 50.

- The most common psychiatric comorbidities were depression and anxiety

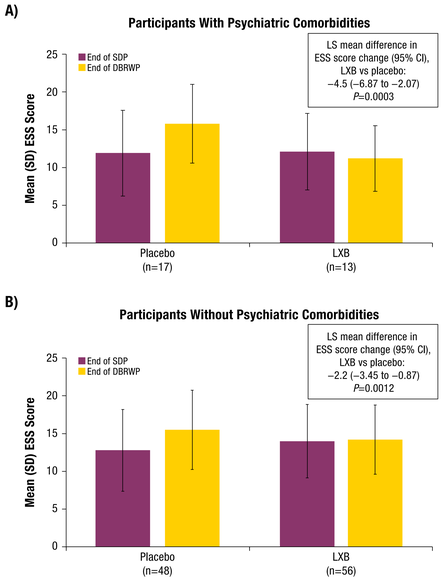
Table 2. Demographics and Other Baseline Characteristics: Subgroups With and Without Psychiatric Comorbidities

Characteristic	With Psychiatric Comorbidities (n=50)	Without Psychiatric Comorbidities (n=151)	Total (N=201)
Age, years, mean (SD)	38.0 (11.27)	36.9 (12.53)	37.2 (12.21)
Female, n (%)	39 (78.0)	83 (55.0)	122 (60.7)
Race, n (%)			
Asian	2 (4.0)	1 (0.7)	3 (1.5)
Black or African American	4 (8.0)	7 (4.6)	11 (5.5)
White	43 (86.0)	134 (88.7)	177 (88.1)
Unknown	1 (2.0)	7 (4.6)	8 (4.0)
Multiple	—	2 (1.3)	2 (1.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (4.0)	16 (10.6)	18 (9.0)
Not Hispanic or Latino	45 (90.0)	124 (82.1)	169 (84.1)
Not Reported	2 (4.0)	9 (6.0)	11 (5.5)
Unknown	0	1 (0.7)	1 (0.5)
Missing	1 (2.0)	1 (0.7)	2 (1.0)
Baseline BMI, kg/m^2, mean (SD)	30.8 (7.04)	28.1 (5.59)	28.8 (6.08)
Region, n (%)			
North America	29 (58.0)	50 (33.1)	79 (39.3)
Europe	21 (42.0)	101 (66.9)	122 (60.7)

BMI, body mass index; SD, standard deviation.

- The majority of participants with psychiatric comorbidities were female (78.0%) and resided in North America (58.0%)

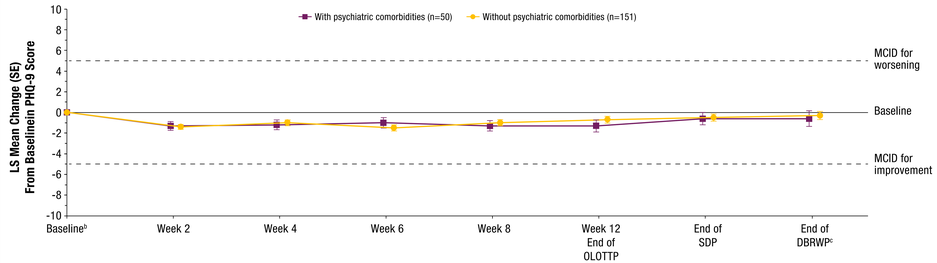
Figure 2. Efficacy of LXB in Participants With (A) and Without (B) Psychiatric Comorbidities[a]



[a]Efficacy population.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; SDP, stable-dose period.

- In both subgroups, compared with participants randomized to LXB, participants randomized to placebo showed worsening (increase) in ESS score from end of SDP to the end of DBRWP

Figure 3. Patient Health Questionnaire–9 in Participants With and Without Psychiatric Comorbidities[a]



[a]Safety population.
[b]Mean scores at baseline were 8.2 for participants with psychiatric comorbidities and 6.4 for participants without psychiatric comorbidities.
[c]Excludes placebo.
DBRWP, double-blind randomized withdrawal period; LS, least squares; MCID, minimum clinically important difference; OLOTTP, open-label optimized treatment and titration period; PHQ-9, Patient Health Questionnaire-9; SDP, stable-dose period; SE, standard error.
P value >0.05 for comparison of groups at all time points.

- Changes in PHQ–9 scores from baseline to various time points throughout the study did not significantly differ between subgroups
  - Participants in both subgroups showed no increases in severity of depressive symptoms from baseline

Table 4. Summary of Treatment-Emergent Adverse Events

Participants, n (%)	With Psychiatric Comorbidities (n=50)	Without Psychiatric Comorbidities (n=151)
With ≥ 1 TEAE	39 (78.0)	114 (75.5)
With a serious TEAE	0	4 (2.6)
With a serious psychiatric-related TEAE	0	1 (0.7)
Confusional state	0	1 (0.7)
Hallucination, visual	0	1 (0.7)
With ≥ 1 TEAE leading to withdrawal	6 (12.0)	15 (9.9)
With ≥ 1 psychiatric-related TEAE leading to withdrawal	3 (6.0)	4 (2.6)
Abnormal sleep-related event	0	1 (0.7)
Anxiety	0	2 (1.3)
Depressed mood	1 (2.0)	1 (0.7)
Depression	1 (2.0)	1 (0.7)
Irritability	0	2 (1.3)
Sleep talking	0	1 (0.7)
Sleep-related eating disorder	1 (2.0)	0

TEAE, treatment-emergent adverse event.

- The safety profile of LXB was similar in patients with and without psychiatric comorbidities

- Two participants had positive C-SSRS responses
  - One participant in the Psychiatric Comorbidities group reported any suicidal ideation or behavior on day 1 and week 4[a]
  - One participant in the Psychiatric Comorbidities group reported any suicidal ideation or behavior at the end of the titration period[b]

[a]This individual's past medical history included anxiety.
[b]This individual's past medical history included depression.
C-SSRS, Columbia Suicide Severity Rating Scale.

Conclusions

- In a phase 3 clinical trial, the safety and efficacy of LXB in participants with narcolepsy were similar, regardless of presence or absence of comorbid psychiatric disorders
- There were no signals that LXB was associated with the emergence of new psychiatric disorders

References: 1. *International Classification of Sleep Disorders – Third Edition*. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** Ruoff CM, Reaven NL, Funk SE, et al. High rates of psychiatric comorbidity in narcolepsy: findings from the Burden Of Narcolepsy Disease (BOND) study of 9,312 patients in the United States. *J Clin Psychiatry*. 2017;78(2):171-176. **3.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **4.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Washington, DC: American Psychiatric Publishing; 2013.

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