004 Efficacy and Safety of Low-Sodium Oxybate in Narcolepsy Patients With/Without Psychiatric/Neurologic Comorbidities

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Introduction

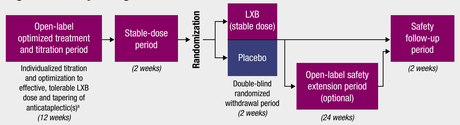
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration for the treatment of cataplexy or excessive daytime sleepiness (EDS) in individuals ≥7 years of age with narcolepsy and for the treatment of idiopathic hypersomnia in adults[1-4]
- A pivotal phase 3, randomized, double-blind, placebo-controlled clinical trial (NCT03030599) demonstrated the efficacy and safety of LXB for the treatment of cataplexy and EDS in adults with narcolepsy[5]
- Previous studies have reported increased incidences of psychiatric and neurologic comorbidities in people with narcolepsy[6-9]
- Evidence demonstrating the efficacy and safety of LXB in people with narcolepsy with comorbid psychiatric and/or neurologic disorders is therefore of interest

Objective

- This post hoc analysis of the phase 3 trial data was conducted to assess the efficacy and safety of LXB treatment in subgroups of participants with narcolepsy with or without psychiatric and/or neurologic comorbidities

Methods

Figure 1. Study Design

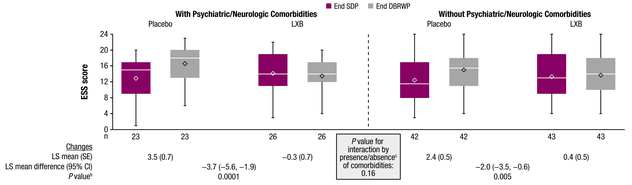


[a]Included selective serotonin-norepinephrine reuptake inhibitors/selective norepinephrine reuptake inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, pitolisant, and antidepressants with other mechanisms of action.
LXB, low-sodium oxybate.

- Eligible participants in the phase 3 study were 18–70 years of age with a diagnosis of narcolepsy with cataplexy (including a history of ≥14 cataplexy attacks over a typical 2-week period, and clinically significant symptoms of excessive daytime sleepiness prior to treatment) based on criteria from the *International Classification of Sleep Disorders – Third Edition*[10] or the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[5,11]
  - In the main study, some psychiatric or neurologic comorbidities were excluded, including history of seizures; current major depression; history or presence of bipolar disorder, bipolar-related disorders, schizophrenia, schizophrenia spectrum disorders, or other DSM-5–defined psychotic disorders; disorders associated with excessive sleepiness; or history or presence of any psychiatric disorder (including active suicidal ideation) or neurological disorder that could have affected the participant's safety and/or interfered with the conduct of the study
- For this analysis, participants with past or concurrent psychiatric and/or neurologic comorbidities were included in the presence subgroup
- The primary efficacy endpoint was the change in weekly number of cataplexy attacks from during the 2 weeks of the stable dose period (SDP) to during the 2 weeks of the double-blind randomized withdrawal period (DBRWP)
- A key secondary efficacy endpoint was the change in the Epworth Sleepiness Scale (ESS) from the end of the SDP to the end of the DBRWP
- The Patient Global Impression of Change was included as an additional efficacy assessment
- Safety assessments included the Patient Health Questionnaire-9 (PHQ-9), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the incidence of treatment-emergent adverse events (TEAEs)
- The safety population includes all participants who took their prescribed LXB regimen for ≥1 night (n=201), and the efficacy population includes all randomized participants who took double-blind study drug and have ≥1 set of post-randomization efficacy assessments (n=134)

Results

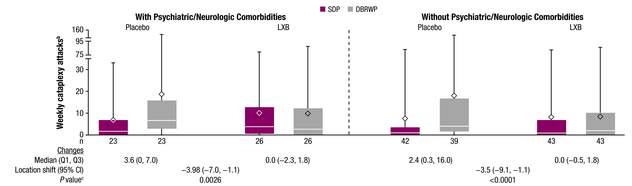
Figure 2. ESS Score in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a]



[a]Efficacy population. [b]*P* values are not adjusted for multiple comparisons. [c]The interaction compares the LXB effect (LS mean difference) in the "with psychiatric/neurologic comorbidities" group with that in the "without psychiatric/neurologic comorbidities" group.
The bottom and top edges of the box indicate the first and third quartiles, the line inside the box is the median, and the diamond marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; SDP, stable-dose period; SE, standard error.

- Participants in both subgroups showed a similar response. Those who were randomized to placebo showed worsening (increase) in their ESS scores, while those who stayed on LXB showed stable ESS scores

Figure 3. Weekly Cataplexy Attacks in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a]



[a]Efficacy population. [b]Cataplexy attacks that occurred during the 2 weeks of the SDP and during the 2 weeks of the DBRWP were analyzed. [c]*P* values are not adjusted for multiple comparisons.
The bottom and top edges of the box indicate the first and third quartiles, the line inside the box is the median, and the diamond marker is the mean. The whiskers extending from the box indicate the minimum and maximum.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; LXB, low-sodium oxybate; Q1, first quartile; Q3, third quartile; SDP, stable-dose period.

- Participants in both subgroups who were randomized to placebo showed an increase in median weekly cataplexy attacks, while those who stayed on LXB showed stable median weekly cataplexy attacks

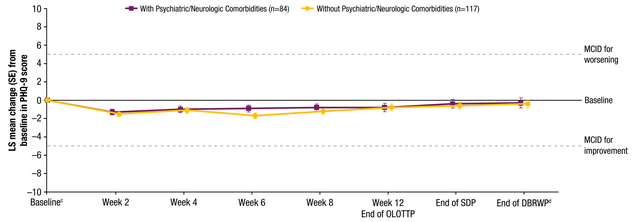
Table 1. Concurrent and Past Psychiatric and/or Neurologic Comorbidities[a]

Concurrent or Past Comorbidity, n (%)[b]	Total (N=84)[c]
Depression	26 (31.0)
Migraine	25 (29.8)
Anxiety	22 (26.2)
Headache	15 (17.9)
Carpal tunnel syndrome	5 (6.0)
Adjustment disorder with depressed mood	4 (4.8)
Attention deficit/hyperactivity disorder	3 (3.6)
Somnambulism	3 (3.6)
Tension headache	3 (3.6)
Cubital tunnel syndrome	2 (2.4)
Paresthesia	2 (2.4)
Restless legs syndrome	2 (2.4)
Trigeminal neuralgia	2 (2.4)

[a]Safety population. [b]The following comorbidities had 1 report each: agoraphobia, anxiety disorder, autism spectrum disorder, borderline personality disorder, complex regional pain syndrome, enuresis, febrile convulsion, insomnia, ischemic stroke, long thoracic nerve palsy, nerve root compression, neuropathy peripheral, nightmare, panic disorder, periodic limb movement disorder, persistent depressive disorder, polyneuropathy, posttraumatic stress disorder, rapid eye movement sleep behavior disorder, sleep-related eating disorder, syncope, vertebral artery dissection. [c]Participants may have reported >1 comorbidity; therefore, total percentage may not equal 100%.

- The most common psychiatric or neurologic comorbidities were depression, migraine, anxiety, headache, carpal tunnel syndrome, and adjustment disorder with depressed mood in ≥5% of people with a psychiatric or neurologic comorbidity

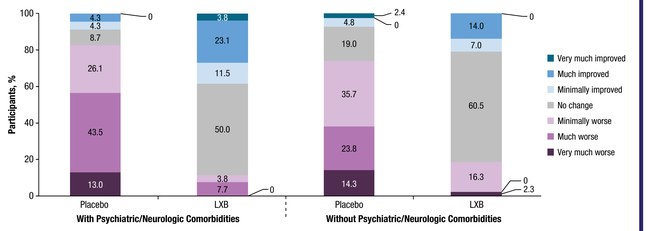
Figure 4. Patient Health Questionnaire–9 Scores in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a,b]



[a]Safety population. [b]PHQ-9 measures the severity of depressive symptoms. [c]Mean scores at baseline were 7.2 for participants with psychiatric and/or neurologic comorbidities and 6.6 for participants without psychiatric and/or neurologic comorbidities. Mean score at baseline was 8.7 for participants with a medical history of depression (10.0 for participants with psychiatric and/or neurologic comorbidities and 7.3 for participants without psychiatric and/or neurologic comorbidities). [d]Excludes placebo. [e]*P*≥0.05 for comparison of groups at all time points. *P* values are not adjusted for multiple comparisons.
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.

- Changes in PHQ–9 scores from baseline to various time points throughout the study did not significantly differ between subgroups[e]
  - There were no increases in severity of depressive symptoms from baseline in either subgroup

Figure 5. Patient Global Impression of Change in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a]



[a]Efficacy population.
LXB, low-sodium oxybate.

- Participants in the placebo groups generally reported worsening while participants in the LXB groups generally reported no change or improvement

- Two participants had C-SSRS positive responses:
  - One participant in the psychiatric and/or neurologic comorbidities subgroup (with a past history of depression) reported a TEAE of depression at week 9 (without concomitant suicidal ideation). This participant reported suicidal ideation on the C-SSRS at week 12 and again during the safety follow-up visit
  - One participant in the psychiatric and/or neurologic comorbidities subgroup reported pre-existing, but not active, suicidal ideation at study day 1. This participant reported suicidal ideation at week 4 and again at the safety follow-up
- No attempted or completed suicides occurred during the trial

C-SSRS data were analyzed from the safety population.
C-SSRS, Columbia-Suicide Severity Rating Scale.

Table 2. Demographics and Other Baseline Characteristics in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a]

Characteristic	With Psychiatric/Neurologic Comorbidities (n=84)	Without Psychiatric/Neurologic Comorbidities (n=117)	Total (N=201)
Age (years), mean (SD)	38.1 (12.1)	36.5 (12.3)	37.2 (12.2)
Female, n (%)	62 (73.8)	60 (51.3)	122 (60.7)
Race, n (%)			
Asian	3 (3.6)	0	3 (1.5)
Black or African American	7 (8.3)	4 (3.4)	11 (5.5)
White	71 (84.5)	106 (90.6)	177 (88.1)
Unknown	3 (3.6)	5 (4.3)	8 (4.0)
Multiple	0	2 (1.7)	2 (1.0)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.6)	15 (12.8)	18 (9.0)
Not Hispanic or Latino	74 (88.1)	95 (81.2)	169 (84.1)
Unknown	1 (1.2)	0	1 (0.5)
Missing	1 (1.2)	1 (0.9)	2 (1.0)
Baseline BMI (kg/m²), mean (SD)	30.5 (6.7)	27.5 (5.3)	28.8 (6.1)
Region, n (%)			
North America	43 (51.2)	36 (30.8)	79 (39.3)
Europe	41 (48.8)	81 (69.2)	122 (60.7)

[a]Safety population.
BMI, body mass index; SD, standard deviation.

- Some imbalances were observed between the subgroups with and without psychiatric/neurologic comorbidities, respectively, with regard to the proportion of participants who were female (73.8% vs 51.3%), Hispanic or Latino (3.6% vs 12.8%), and from North America (51.2% vs 30.8%), and in terms of mean body mass index (30.5 vs 27.5 kg/m²)

Table 3. Summary of Treatment-Emergent Adverse Events in Participants With and Without Psychiatric and/or Neurologic Comorbidities[a]

Participants, n (%)[b]	With Psychiatric/ Neurologic Comorbidities (n=84)	Without Psychiatric/ Neurologic Comorbidities (n=117)	Total (N=201)
With ≥1 TEAE	69 (82.1)	84 (71.8)	153 (76.1)
With ≥1 psychiatric and/or neurologic TEAE	55 (65.5)	63 (53.8)	118 (58.7)
With ≥1 TEAE related to treatment	36 (42.9)	49 (41.9)	85 (42.3)
With ≥1 serious TEAE	1 (1.2)	3 (2.6)	4 (2.0)
With ≥1 serious psychiatric and/or neurologic TEAE	0	1 (0.9)	1 (0.5)
Confusional state	0	1 (0.9)	1 (0.5)
Hallucination, visual	0	1 (0.9)	1 (0.5)
Peripheral nerve paresis	0	1 (0.9)	1 (0.5)
With ≥1 TEAE leading to withdrawal	12 (14.3)	9 (7.7)	21 (10.4)
With ≥1 psychiatric and/or neurologic TEAE leading to withdrawal	10 (11.9)	8 (6.8)	18 (9 .0)
Cataplexy	3 (3.6)	4 (3.4)	7 (3.5)
Cognitive disorder	1 (1.2)	0	1 (0.5)
Headache	1 (1.2)	1 (0.9)	2 (1.0)
Somnolence	0	1 (0.9)	1 (0.5)
Abnormal sleep-related event	0	1 (0.9)	1 (0.5)
Anxiety	1 (1.2)	1 (0.9)	2 (1.0)
Depressed mood	2 (2.4)	0	2 (1.0)
Depression	2 (2.4)	0	2 (1.0)
Irritability	1 (1.2)	1 (0.9)	2 (1.0)
Sleep talking	0	1 (0.9)	1 (0.5)
Sleep-related eating disorder	1 (1.2)	0	1 (0.5)

[a]Safety population. [b]Note that participants could have reported ≥1 TEAE within a system organ class or preferred term.
TEAE, treatment-emergent adverse event.

Conclusions

- In this analysis, the efficacy and safety of LXB were consistent in the presence or absence of past or concurrent psychiatric and/or neurologic comorbidities
- This analysis is limited in that it is post hoc and involves a small number of participants; the study excluded participants with certain, more severe psychiatric or neurologic comorbidities, which limits the generalizability of the findings
- The safety profile for both subgroups was consistent with the known safety profile of LXB

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **3.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **4.** US Food and Drug Administration. Quantitative labeling of sodium, potassium, and phosphorus for human over-the-counter and prescription drug products. Guidance for industry. 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **5.** Bogan RK, et al. *Sleep.* 2021;44(3):zsaa206. **6.** Ruoff CM, et al. *J Clin Psychiatry.* 2017;78(2):171-176. **7.** Morse AM, et al. *Med Sci (Basel).* 2018;6(1):16. **8.** Jennum P, et al. *Sleep.* 2013;36(6):835-840. **9.** Black J, et al. *Sleep Med.* 2017;33:13-18. **10.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **11.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013.

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