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Efficacy and Safety of Low-Sodium Oxybate in Participants With Idiopathic Hypersomnia With and Without Psychiatric Comorbidities

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Introduction

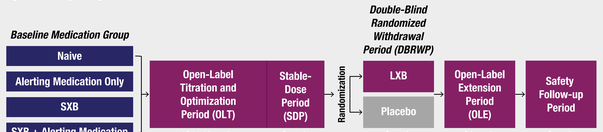
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat idiopathic hypersomnia in adults, and excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy[1-4]
- A pivotal phase 3, randomized, double-blind, placebo-controlled clinical trial (NCT03533114) demonstrated the efficacy and safety of LXB in treating adults with idiopathic hypersomnia[5]
- Idiopathic hypersomnia is associated with psychiatric comorbidities (eg, anxiety and depression prevalences of 31%–41%)[6,7]; people with idiopathic hypersomnia also have greater odds of psychiatric comorbidities compared with matched controls[8]
- Evidence demonstrating the efficacy and safety of LXB in individuals with idiopathic hypersomnia with comorbid psychiatric disorders is therefore needed

Objective

- This post hoc analysis of the phase 3 trial data assessed the efficacy and safety of LXB treatment in groups of participants with idiopathic hypersomnia with and without psychiatric comorbidities

Methods

Figure 1. Study Design



LXB, low-sodium oxybate; SXB, sodium oxybate.

- Eligible participants in the phase 3 study were 18–75 years of age and had an idiopathic hypersomnia diagnosis based on criteria from the *International Classification of Sleep Disorders – Second Edition* or *Third Edition*[5,9,10]
  - Participants were excluded if their hypersomnia resulted from a psychiatric disorder or if they had a current or past (within 1 year) major depressive episode, based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*[11] (DSM-5), or history or presence of bipolar and related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria
  - Participants were allowed if their depression was adequately managed, as judged by the investigator or treating clinician, and their antidepressant treatment had been stable for ≥6 months before screening and remained stable for the duration of the study
- For this analysis, participants with past or concurrent psychiatric comorbidities were included in the "Presence" group
- The primary efficacy endpoint was change in Epworth Sleepiness Scale (ESS) score from the end of the stable-dose period (SDP) to the end of the double-blind randomized withdrawal period (DBRWP), while key secondary efficacy endpoints included change in Idiopathic Hypersomnia Severity Scale (IHSS) score from end of SDP to end of DBRWP and number of participants who reported symptom worsening (*minimally, much,* or *very much worse*) on the Patient Global Impression of Change (PGIc) at end of DBRWP
- An exploratory efficacy endpoint was change in mean daily Visual Analog Scale for Sleep Inertia (VAS-SI) score from last week of SDP to last week of DBRWP
- Safety assessments included the Columbia-Suicide Severity Rating Scale (C-SSRS) and incidence of treatment-emergent adverse events (TEAEs)
- The safety population included all participants who received ≥1 dose of study drug; the efficacy population included all randomized participants who took ≥1 dose of double-blind study drug and had ≥1 set of post-randomization efficacy assessments

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2023. **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.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **6.** Nevsimalova S, et al. *Brain Sci.* 2022;12(11):1491. **7.** Saad R, et al. *Sleep Epidemiol.* 2023;3:100059. **8.** Lillaney P, et al. Presented at: Annual Meeting of the Associated Professional Sleep Societies; June 3-7, 2023; Indianapolis, IN. **9.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **10.** American Academy of Sleep Medicine. *The International Classification of Sleep Disorders: Diagnostic & Coding Manual – Second Edition.* Westchester, IL: American Academy of Sleep Medicine; 2005. **11.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013.

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Disclosures: C Chepke has served on advisory boards for AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Idorsia, Intra-Cellular, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, and Teva; has served as a consultant for AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, and Teva; has received grant/research support from Acadia, Axsome, Harmony, Neurocrine, and Teva; and has served on speakers bureaus for AbbVie, Acadia, Alkermes, Axsome, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, and Teva. His spouse has served on advisory boards for Bristol Myers Squibb and Otsuka. **M Whalen, DS Fuller, SL Bronson,** and **JK Alexander** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **DT Plante** is a consultant and advisory board member for Jazz Pharmaceuticals. He has also served as a consultant/advisory board member for Alkermes, Harmony Biosciences, Takeda, and Centessa and a consultant for Aditum Bio, LLC, and Teva Pharmaceuticals (Australia).

Results

Table 1. Past and Concurrent Psychiatric Comorbidities

	Total[a] (N=154)
Past or concurrent psychiatric comorbidity,[b] n(%)	68 (44.2)
Anxiety	35 (22.7)
Depression	35 (22.7)
Attention-deficit/hyperactivity disorder	10 (6.5)
Generalized anxiety disorder	3 (1.9)
Major depression	3 (1.9)
Adjustment disorder	2 (1.3)
Adjustment disorder with depressed mood	2 (1.3)
Panic attack	2 (1.3)
Posttraumatic stress disorder	2 (1.3)
Autism spectrum disorder	1 (0.6)
Claustrophobia	1 (0.6)
Obsessive-compulsive disorder	1 (0.6)
Perinatal depression	1 (0.6)
Social anxiety disorder	1 (0.6)

Participants may have reported multiple conditions; individual condition percentages will not sum to total psychiatric comorbidity percentage.
[a]Safety population; includes all participants who took ≥1 dose of study drug.
[b]Participants with past or concurrent psychiatric comorbidities were included in Presence group using MedDRA System Organ Class and Preferred Term definitions.

- The most common psychiatric comorbidities (≥5% of participants) were anxiety, depression, and attention-deficit/hyperactivity disorder

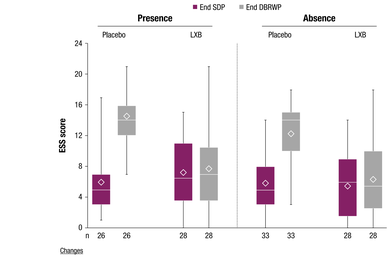
Table 2. Demographic and Other Baseline Characteristics by Presence/Absence of Psychiatric Comorbidities[a]

Characteristic	Presence (n=68)	Absence (n=86)	Total (N=154)
Age, years, mean (SD)	40.5 (13.4)	40.1 (14.1)	40.3 (13.7)
Female, n (%)	52 (76.5)	53 (61.6)	105 (68.2)
Race			
Black or African American	4 (5.9)	5 (5.8)	9 (5.8)
Native Hawaiian or other Pacific Islander	0	1 (1.2)	1 (0.6)
White	62 (91.2)	67 (77.9)	129 (83.8)
Unknown	2 (2.9)	12 (14.0)	14 (9.1)
Multiple	0	1 (1.2)	1 (0.6)
Ethnicity			
Hispanic or Latino	3 (4.4)	13 (15.1)	16 (10.4)
Not Hispanic or Latino	64 (94.1)	60 (69.8)	124 (80.5)
Unknown	1 (1.5)	13 (15.1)	14 (9.1)
BMI, kg/m², mean (SD)	28.9 (9.1)	26.2 (5.5)	27.4 (7.4)
Region			
North America	58 (85.3)	46 (53.5)	104 (67.5)
Europe	10 (14.7)	40 (46.5)	50 (32.5)
ESS scores at baseline[b]			
Mean (SD)	16.1 (3.2)	15.4 (4.2)	15.7 (3.8)
Median	16.0	16.0	16.0
IHSS total scores at baseline[b]			
Mean (SD)	34.2 (7.6)	29.3 (8.3)	31.6 (8.3)
Median	34.0	31.0	33.0
VAS-SI score at baseline[c]			
Mean (SD)	58.1 (22.9)	51.0 (27.4)	54.4 (25.5)
Median	61.7	54.0	56.4

[a]Safety population; includes all participants who took ≥1 dose of study drug. [b]Presence group, n=54; Absence group, n=61; total, n=115. [c]Presence group, n=55; Absence group, n=50; total, n=105.
BMI, body mass index; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; VAS-SI, Visual Analog Scale for Sleep Inertia.

- Of the 154 participants enrolled, most were female (68%) and White (84%); 6 participants were taking high-sodium oxybate at study entry

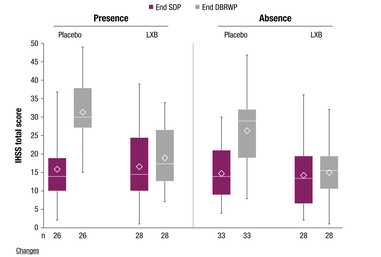
Figure 2. Epworth Sleepiness Scale Score by Presence/Absence of Psychiatric Comorbidities[a]



[a]Efficacy population; includes all randomized participants who took ≥1 dose of double-blind study drug and had ≥1 set of post-randomization efficacy assessments. [b]Interaction compares effect of LXB (LS mean difference) in Presence group with that in Absence group. Bottom and top edges of box indicate first and third quartiles, line inside box is median, and diamond marker inside box is mean. Whiskers extending from box indicate minimum and maximum.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; SD, standard deviation; SDP, stable-dose period; SE, standard error.

- Participants with and without psychiatric comorbidities had similar responses: participants randomized to placebo showed worsening (increases) in ESS scores, while participants who continued LXB had stable ESS scores

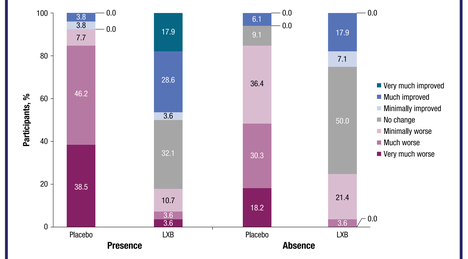
Figure 3. Idiopathic Hypersomnia Severity Scale Total Score by Presence/Absence of Psychiatric Comorbidities[a]



[a]Efficacy population; includes all randomized participants who took ≥1 dose of double-blind study drug and had ≥1 set of post-randomization efficacy assessments. [b]Interaction compares effect of LXB (LS mean difference) in Presence group with that in Absence group. Bottom and top edges of box indicate first and third quartiles, line inside box is median, and diamond marker inside box is mean. Whiskers extending from box indicate minimum and maximum.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least squares; LXB, low-sodium oxybate; SD, standard deviation; SDP, stable-dose period; SE, standard error.

- Participants with and without psychiatric comorbidities had similar responses: participants randomized to placebo showed worsening (increases) in IHSS scores, while participants who continued LXB had stable IHSS scores

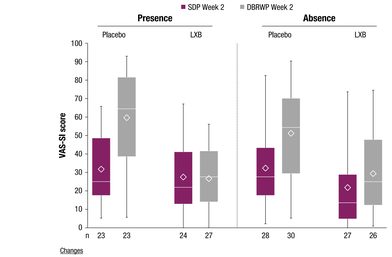
Figure 4. Patient Global Impression of Change by Presence/Absence of Psychiatric Comorbidities[a]



[a]Efficacy population; includes all randomized participants who took ≥1 dose of double-blind study drug and had ≥1 set of post-randomization efficacy assessments. LXB, low-sodium oxybate.

- Participants randomized to placebo in the DBRWP generally reported worsening, while participants randomized to LXB generally reported improvement or no change on the PGIc (Presence, $P<0.0001$; Absence, $P<0.0001$)
  - In participants with psychiatric comorbidities, the proportion who reported worse PGIc status (*minimally worse, much worse,* and *very much worse*) was 5.2-fold higher among those who were randomized to placebo than among those randomized to LXB
  - In participants without psychiatric comorbidities, the proportion who reported worse PGIc status was 3.4-fold higher among those who were randomized to placebo than among those randomized to LXB

Figure 5. Visual Analog Scale for Sleep Inertia Score by Presence/Absence of Psychiatric Comorbidities[a]



[a]Efficacy population; includes all randomized participants who took ≥1 dose of double-blind study drug and had ≥1 set of post-randomization efficacy assessments. [b]Interaction compares effect of LXB (LS mean difference) in Presence group with that in Absence group. Bottom and top edges of box indicate first and third quartiles, line inside box is median, and diamond marker inside box is mean. Whiskers extending from box indicate minimum and maximum.
CI, confidence interval; DBRWP, double-blind randomized withdrawal period; LS, least squares; LXB, low-sodium oxybate; SD, standard deviation; SDP, stable-dose period; SE, standard error; VAS-SI, Visual Analog Scale for Sleep Inertia.

- Participants with and without psychiatric comorbidities randomized to placebo showed worsening (increases) in VAS-SI score from SDP week 2 to DBRWP week 2, while participants who continued LXB had stable VAS-SI scores

Table 3. Summary of Treatment-Emergent Adverse Events by Presence/Absence of Psychiatric Comorbidities[a]

Participants, n (%)	Presence (n=68)	Absence (n=86)	Total (N=154)
With ≥1 TEAE	61 (89.7)	62 (72.1)	123 (79.9)
With ≥1 serious TEAE[b]	1 (1.5)	3 (3.5)	4 (2.6)
With ≥1 TEAE leading to discontinuation	11 (16.2)	15 (17.4)	26 (16.9)
With ≥1 psychiatric TEAE leading to withdrawal	7 (10.3)	6 (7.0)	13 (8.4)
Anxiety	2 (2.9)	2 (2.3)	4 (2.6)
Apathy	1 (1.5)	0	1 (0.6)
Confusional arousal	1 (1.5)	0	1 (0.6)
Confusional state	0	1 (1.2)	1 (0.6)
Decreased interest	1 (1.5)	0	1 (0.6)
Hallucination, visual	0	1 (1.2)	1 (0.6)
Insomnia	1 (1.5)	2 (2.3)	3 (1.9)
Irritability	0	1 (1.2)	1 (0.6)
Panic attack	1 (1.5)	0	1 (0.6)
Somnambulism	1 (1.5)	0	1 (0.6)
Psychiatric TEAEs occurring in ≥5% of participants			
Anxiety[c]	12 (17.6)	5 (5.8)	17 (11.0)
Insomnia	5 (7.4)	6 (7.0)	11 (7.1)

[a]Safety population; includes all participants who took ≥1 dose of study drug. [b]Serious TEAEs included non-cardiac chest pain, pyelonephritis, rhabdomyolysis, syncope, and nephrolithiasis, which investigator deemed were unrelated to study drug. [c]Among the 17 reported TEAEs of anxiety, 11 were deemed related to study drug, 15 cases resolved (no study drug change, n=8; dose reduced, n=2; drug interrupted, n=1; drug withdrawn, n=4).
TEAE, treatment-emergent adverse event.

- No serious psychiatric TEAEs were reported
- The majority of TEAEs of anxiety (15/17) were resolved; 4 participants discontinued study drug because of a TEAE of anxiety
  - Two unresolved cases of anxiety (1 participant from each group) were deemed unrelated to LXB treatment; these participants continued LXB

- Throughout the study, no participants with psychiatric comorbidities reported any suicidal ideation on the C-SSRS
  - One participant in the group without psychiatric comorbidities reported suicidal ideation on the C-SSRS at the end of the titration period (week 14); this participant withdrew from the study at that time because of a TEAE of paresthesia (deemed unrelated to study drug), and the participant's C-SSRS on safety follow-up was negative for suicidal ideation
  - There were no other reports for participants in either group at any other point during the study, and there were no attempted or completed suicides during the trial

Conclusions

- In this post hoc analysis of participants with idiopathic hypersomnia, the efficacy and safety of LXB were similar in participants with and without psychiatric comorbidities
- There were no serious psychiatric safety signals; anxiety was the most common psychiatric-related TEAE for which the majority of events were managed/resolved on treatment
  - The main study's exclusion of participants with certain more severe psychiatric comorbidities limited the findings and thus affected their generalizability
- Given the high prevalence of psychiatric comorbidities in patients with idiopathic hypersomnia, it is important to understand treatment effects and long-term health outcomes in this population

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