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Long-term Safety During a Clinical Trial of Lower-Sodium Oxybate in Participants With Narcolepsy With Cataplexy

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Introduction

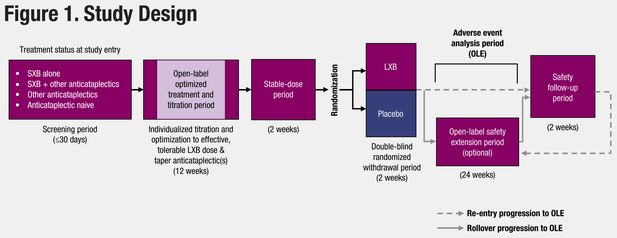
- Sodium oxybate (SXB; Xyrem®) is strongly recommended by the American Academy of Sleep Medicine for the treatment of narcolepsy due to its efficacy in improving cataplexy and excessive daytime sleepiness[1]
- Lower-sodium oxybate (LXB; Xywav®) contains the same active moiety as SXB, with 92% less sodium, and is approved in the United States (US) for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and idiopathic hypersomnia in adults[2,3]
  - LXB has been recognized by the US Food and Drug Administration (FDA) in the narcolepsy population for its significant reduction in chronic sodium burden compared with SXB, which "will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated"[4]
- The efficacy and safety of LXB for the treatment of narcolepsy with cataplexy were established in a phase 3, placebo-controlled, double-blind, randomized withdrawal study (NCT03030599; results presented elsewhere)[2]
  - During open-label treatment with LXB in the main study, most treatment-emergent adverse events (TEAEs) were consistent with the known safety profile of SXB,[5] occurred early on, and were generally of short duration; participants previously taking SXB reported fewer TEAEs overall than oxybate-naive participants[6]

Objective

- This analysis evaluated TEAEs during a 6-month open-label extension (OLE) of the phase 3 study of LXB in adults with narcolepsy with cataplexy

Methods

Figure 1. Study Design



OLE, open-label extension; LXB, lower-sodium oxybate; SXB, sodium oxybate.

- Adults 18–70 years of age with a primary diagnosis of narcolepsy with cataplexy based on criteria from the *International Classification of Sleep Disorders*, 3rd Edition[7] or *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition[8] were eligible to participate
  - At study entry, participants may have been taking SXB and/or other anticataplectic medications (primarily antidepressants), or were cataplexy treatment naive
- Participants entered a 12-week, open-label, optimized treatment and titration period (OLOTTP) with initiation and titration of LXB oral solution occurring alongside tapering and discontinuation of any prior other anticataplectic treatments; OLOTTP was followed by a 2-week stable-dose period (SDP), a 2-week placebo-controlled, double-blind, randomized withdrawal period (DBRWP), and an optional 24-week (6-month) open-label safety extension (OLE)
- Participants entered OLE by 1 of 2 routes, depending on whether they completed the main study before or after a protocol amendment that added the OLE
  - Re-entry: after discontinuing LXB treatment at the end of the main study, participants were rescreened for up to 30 days, then initiated LXB (4.5 g/night) or, if taking SXB during rescreening, transitioned to identical LXB doses (gram-for-gram). Any other anticataplectics taken during rescreening were to be tapered and discontinued by OLE week 12
  - Rollover: directly after completing the main study, participants initiated LXB at a dose no more than half that at the end of SDP
- All OLE participants could titrate the dose of LXB (at a rate of 1–1.5 g/night/week) to a maximum of 9 g/night
- TEAEs were evaluated in the safety population (received ≥1 study drug dose) during OLE
- TEAE duration represents time from TEAE start to end date (or end of OLE, if TEAE end date unrecorded)

Results

Table 1. Demographics and Baseline Characteristics in the OLE[a]

Characteristic	Re-entry (n=27)	Rollover (n=47)	Total (N=74)
Age, years			
Mean (SD)	42.2 (11.8)	35.0 (12.5)	37.6 (12.6)
Median (range)	41.0 (23, 68)	33.0 (18, 70)	38.0 (18, 70)
Sex, n (%)			
Female	20 (74.1)	29 (61.7)	49 (66.2)
Male	7 (25.9)	18 (38.3)	25 (33.8)
Race, n (%)			
White	26 (96.3)	42 (89.4)	68 (91.9)
Black or African American	0	5 (10.6)	5 (6.8)
Missing	1 (3.7)	0	1 (1.4)
Region, n (%)			
Europe	24 (88.9)	17 (36.2)	41 (55.4)
North America	3 (11.1)	30 (63.8)	33 (44.6)
Days from end of main study to OLE day 1			
Mean (SD)	16.6 (7.3)	1.0 (0)	6.7 (8.8)
Median (range)	15 (4.0, 33.0)	1 (1.0, 1.0)	1 (1.0, 33.0)

OLE, open-label extension; SD, standard deviation.
[a]OLE safety population (participants who received ≥1 dose of study drug during OLE).

- Re-entry and rollover participants were demographically similar except that the majority of re-entry participants were from Europe, whereas the majority of rollover participants were from North America
- Most participants who re-entered into OLE did so within 1 month after the end of the main study
- In participants taking LXB during DBRWP who entered OLE, the mean (SD) total LXB dose at DBRWP was 6.93 (1.44) g/night and 7.38 (1.48) g/night for re-entry (n=15) and rollover (n=28) participants, respectively, and the mean (SD) total LXB dose at OLE entry was 6.30 (1.44) g/night and 7.33 (1.5) g/night, respectively

Table 2. Peak Incidence and Duration of TEAEs Occurring in ≥5% of Participants During the OLE[a]

TEAE	Participants With TEAE, n (%)	Peak Incidence[b]	Median Duration of Event (Range)
Headache	7 (9.5)	Month 3	1.0 (1, 25) day
Nasopharyngitis	6 (8.1)	Month 6	9.0 (1, 24) days
Dizziness	5 (6.8)	Month 1	26.0 (1, 181) days

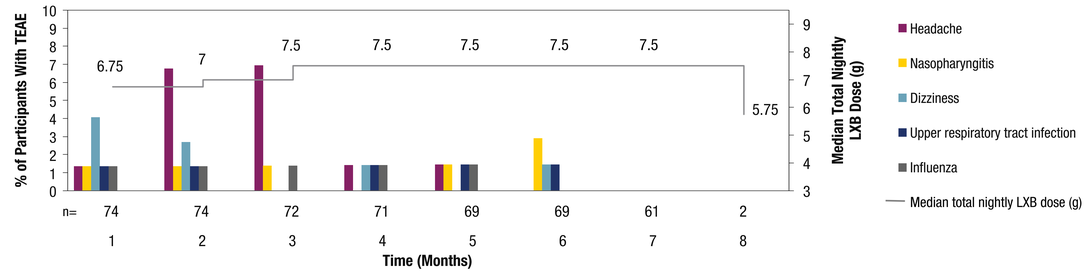
OLE, open-label extension; TEAE, treatment-emergent adverse event.
[a]OLE safety population (participants who received ≥1 dose of study drug).
[b]Defined as the month with the highest percentage of participants reporting the TEAE.

- Of note, no participant reported a TEAE of fall or enuresis; 1 participant reported nausea (rollover)

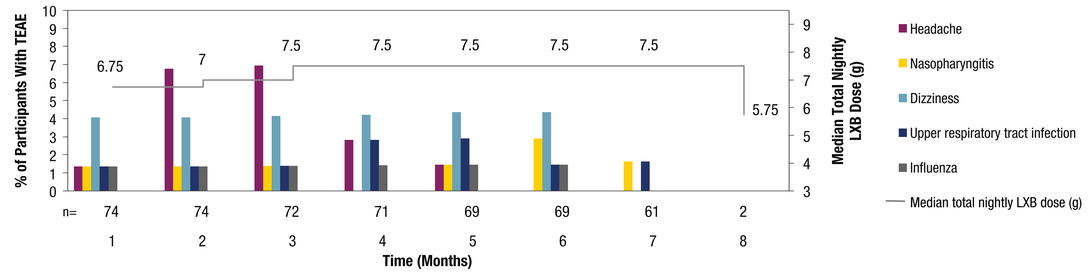
- Most TEAEs were mild or moderate; 2 participants had severe TEAEs (invasive ductal breast carcinoma, n=1; dizziness, n=1)
- One participant had a serious TEAE (invasive ductal breast carcinoma)
- Few participants (14.9%) had LXB-related TEAEs, most frequently dizziness (overall, 5.4%; re-entry, 7.4%; rollover, 4.3%)
- LXB-related TEAEs were more common in participants who re-entered (re-entry, 22.2%; rollover, 10.6%)
- Seven participants discontinued (re-entry, n=2; rollover, n=5)
  - 3 due to TEAEs (invasive ductal breast carcinoma, n=1; apathy, n=1; sleep apnea syndrome, n=1); only apathy was treatment related
  - 2 lost to follow-up
  - 1 due to lack of efficacy
  - 1 other

Figure 2. New and Continuing TEAEs Each Month During the OLE[a,b]

New TEAEs



Continuing TEAEs[c]



LXB, lower-sodium oxybate; OLE, open-label extension; TEAE, treatment-emergent adverse event.
[a]OLE safety population (participants who received ≥1 dose of study drug).
[b]Participants reporting >1 TEAE term per month were counted only once within that month.
[c]Includes all participants experiencing a TEAE at each study time point, regardless of the month of TEAE onset.

- New TEAEs were most prevalent in month 2 (10/74 [13.5%] participants reported a TEAE)
- Continuing TEAEs were most prevalent in month 3 (11/72 [15.3%] participants reported a TEAE)

Table 3. TEAEs Occurring in >1 Participant in the OLE[a]

n (%)	Re-entry (n=27)	Rollover (n=47)	Total (N=74)
Participants with ≥1 TEAE	16 (59.3)	27 (57.4)	43 (58.1)[b]
Participants with ≥1 TEAE related to LXB	6 (22.2)	5 (10.6)	11 (14.9)
Headache	4 (14.8)	3 (6.4)	7 (9.5)
Nasopharyngitis	3 (11.1)	3 (6.4)	6 (8.1)
Dizziness	3 (11.1)	2 (4.3)	5 (6.8)
Influenza	0	4 (8.5)	4 (5.4)
Upper respiratory tract infection	1 (3.7)	3 (6.4)	4 (5.4)
Anxiety	1 (3.7)	2 (4.3)	3 (4.1)
Dysmenorrhea	2 (7.4)	1 (2.1)	3 (4.1)
Rhinitis	1 (3.7)	2 (4.3)	3 (4.1)
Abdominal pain	0	2 (4.3)	2 (2.7)
Diarrhea	2 (7.4)	0	2 (2.7)
Fatigue	1 (3.7)	1 (2.1)	2 (2.7)
Nasal congestion	0	2 (4.3)	2 (2.7)
Oropharyngeal pain	1 (3.7)	1 (2.1)	2 (2.7)
Urinary tract infection	1 (3.7)	1 (2.1)	2 (2.7)

LXB, lower-sodium oxybate; OLE, open-label extension; TEAE, treatment-emergent adverse event.
[a]OLE safety population (participants who received ≥1 dose of study drug during OLE).
[b]Compared with 76.1% (153/201) during the main study.

Conclusions

- In this long-term study of LXB, safety and tolerability profiles during OLE were generally consistent with the main study period and the known safety profile of SXB[5]
- The most common TEAEs were headache, nasopharyngitis, and dizziness; these events occurred early on and were generally of short duration
- Most TEAEs were mild or moderate in severity
  - All TEAEs except nasopharyngitis and upper respiratory tract infection resolved
  - No participant reported a TEAE of fall or enuresis; 1 participant reported nausea (rollover)

References: 1. Maski K, et al. *J Clin Sleep Med.* 2021;17:1881-93. **2.** Bogan RK, et al. *Sleep.* 2021;44:zsaa206. **3.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **4.** Food and Drug Administration. Clinical superiority findings. 2021. Available at: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. **5.** XYREM® (sodium oxybate) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **6.** Bogan RK, et al. Presented at: Annual Meeting of the Associated Professional Sleep Societies; June 10-13, 2021. **7.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **8.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013:372-8.

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Disclosures: RK Bogan is a shareholder of Watermark Medical and Healthy Humming, LLC; serves on the board of directors for Watermark; is a medical consultant to Jazz Pharmaceuticals, Harmony Biosciences, Avadel Pharmaceuticals, Takeda, and Oventus; has conducted industry-funded research for Avadel, Axsome, Bresotec, Bayer, Idorsia, Suven, Jazz, Balance, NLS, Vanda, Merck, Eisai, Philips, Fresca, Takeda, LivaNova, Roche, Sanofi, Sommetrics, and Noctrix; and is on the speakers bureau for Jazz, Eisai, and Harmony. **N Foldvary-Schaefer** has served on an advisory committee for Jazz Pharmaceuticals and participated in clinical trials supported by Jazz Pharmaceuticals, Suven, and Takeda. **R Skowronski** and **A Chen** 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. **MJ Thorpy** has received research/grant support and consultancy fees from Jazz Pharmaceuticals, Harmony Biosciences, Balance Therapeutics, Axsome Therapeutics, and Avadel Pharmaceuticals.

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