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

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Introduction

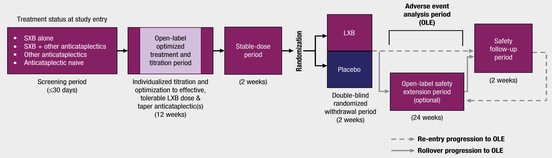
- High-sodium oxybate (SXB) is strongly recommended by the American Academy of Sleep Medicine for the treatment of narcolepsy due to its efficacy in improving cataplexy and excessive daytime sleepiness[1]
- Low-sodium oxybate (LXB) contains the same active moiety as SXB, with 92% less sodium, and is 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[2-6]
  - LXB has been recognized by the US Food and Drug Administration (FDA) in the narcolepsy population for its greatly reduced chronic sodium burden compared with SXB, which is clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated[7]
- 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,[8] occurred early on, and were generally of short duration; participants previously taking SXB reported fewer TEAEs overall than oxybate-naive participants[9]

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, low-sodium oxybate; SXB, high-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[10] or *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition[11] 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)

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

- 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

[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.
OLE, open-label extension; TEAE, treatment-emergent adverse event.

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

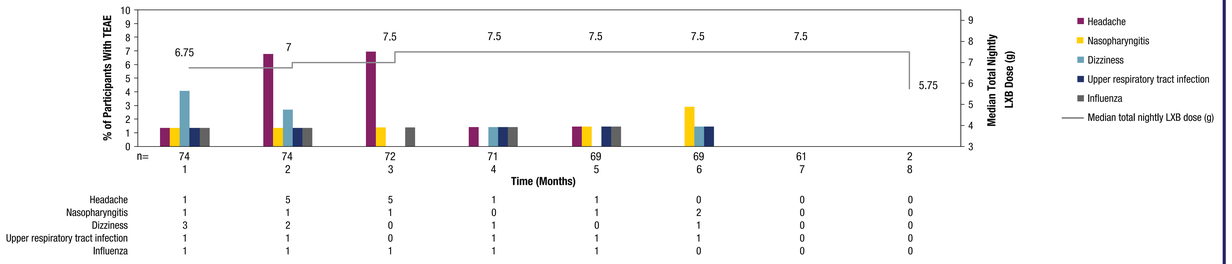
Table 3. TEAEs Occurring in >1 Participant in the OLE[a]

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)

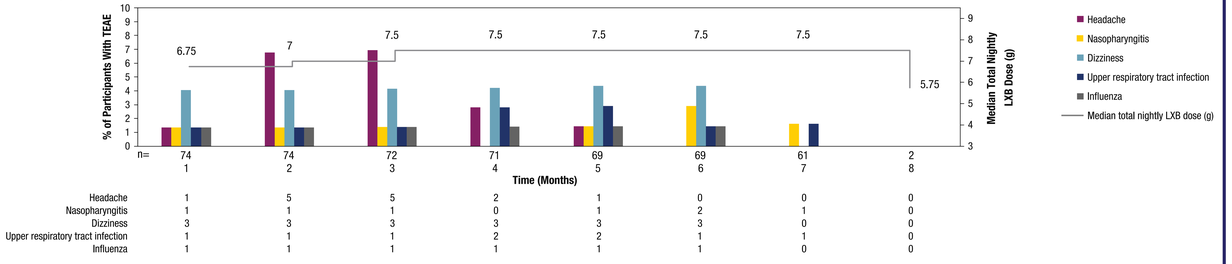
[a]OLE safety population (participants who received ≥1 dose of study drug during OLE). [b]Compared with 76.1% (153/201) during the main study.
LXB, low-sodium oxybate; OLE, open-label extension; TEAE, treatment-emergent adverse event.

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

New TEAEs



Continuing TEAEs[c]



[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.
LXB, low-sodium oxybate; OLE, open-label extension; TEAE, treatment-emergent adverse event.

- New TEAEs were most prevalent in month 2 (10/74 [13.5%] participants reported a TEAE), with headache being the most frequently reported TEAE
- Continuing TEAEs were most prevalent in month 3 (11/72 [15.3%] participants reported a TEAE), with headache and dizziness being the most frequently reported TEAEs

- 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

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[8]
- 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)

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