001 Effects of Low-Sodium Oxybate on 24-Hour Total Sleep Time: Data From a Phase 3 Clinical Study in Adults With Idiopathic Hypersomnia

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Introduction

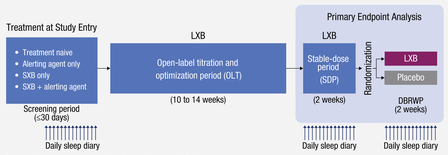
- Idiopathic hypersomnia is a debilitating central hypersomnolence disorder characterized by excessive daytime sleepiness (EDS), with severe sleep inertia and long nocturnal sleep time as key symptoms[1-3]
- The first approved treatment for idiopathic hypersomnia in the US is low-sodium oxybate (LXB; Xywav®)
  - LXB is indicated for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy, and idiopathic hypersomnia in adults[4-7]
- The efficacy and safety of LXB for the treatment of idiopathic hypersomnia were established in a phase 3, double-blind, randomized withdrawal study (NCT03533114)[8]

Objective

- This analysis evaluated the effect of LXB treatment on 24-hour total sleep time (TST) in participants with idiopathic hypersomnia in this phase 3 study

Methods

Figure 1. Study Design



DBRWP, double-blind randomized withdrawal period; LXB, low-sodium oxybate; SXB, high-sodium oxybate.

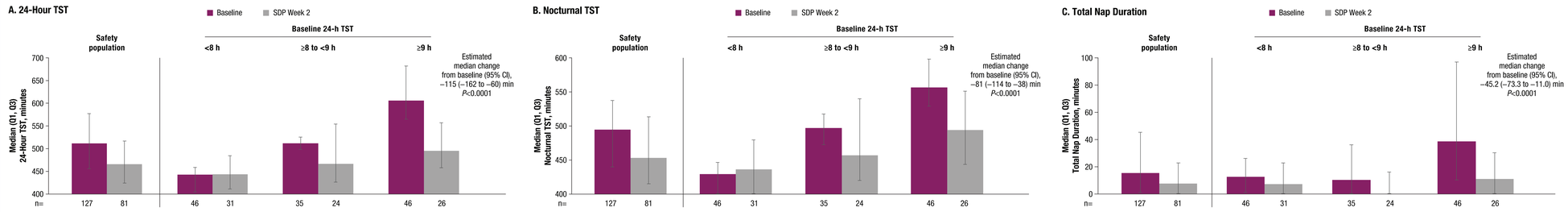
- Eligible participants were adults (18–75 years of age) with a primary diagnosis of idiopathic hypersomnia according to *International Classification of Sleep Disorders*, 2nd or 3rd Edition criteria and an average nocturnal TST of at least 7 hours[8]
  - Participants were either treatment naive or were taking medications for idiopathic hypersomnia symptoms, including high-sodium oxybate (SXB; Xyrem®) and/or alerting agents (AAs; stimulants or wake-promoting agents)[8]
  - Participants taking AAs were required to have been taking the same dose and regimen for ≥2 months before screening and to take the same dose throughout the study[8]
- Daily sleep time was collected using a participant-recorded daily electronic sleep diary for at least 2 weeks during the screening period and each day during the 2-week stable-dose period (SDP) and the 2-week double-blind randomized withdrawal period (DBRWP)[8]
- This post hoc analysis of sleep parameters was performed using daily sleep diary data
  - Assessments included 24-hour TST (nocturnal TST plus duration of nap[s]), nocturnal TST (time from trying to sleep until final awakening, subtracting duration of awakenings at night), and duration of naps
- Data were analyzed using each participant's averaged values derived from screening week 2 (baseline), SDP week 2, and DBRWP week 2
- A subgroup analysis was performed on participants with higher, medium, and lower baseline 24-hour TST
  - Due to data skewness, nonparametric methods were adopted. Significance was tested via rank-based analysis of covariance, and the 95% CI was obtained from Hodges-Lehmann estimate

Table 1. Sleep Diary Questions

Question	Sample Replies
What time did you get into bed?	9:55 PM
What time did you try to go to sleep?	10:30 PM
How long did it take you to fall asleep?	20 minutes
How many times did you wake up, not counting your final awakening?	2 times
In total, how long did these awakenings last?	30 minutes
Was there anything unusual that affected your sleep last night? (Yes/No) If yes, please explain.	I have a cold
What time was your final awakening?	7:00 AM
What time did you get out of bed for the day?	7:45 AM
Is today an off day (eg, non-working day/weekend or holiday)? (Yes/No)	No
How many times did you nap or doze during the day?	2 times
In total, how long did you nap or doze during the day? (Add up all naps if you had more than one)	1 hour, 10 minutes
Was there anything unusual about your naps today? (Yes/No) If yes, please explain.	Noise from construction next door interrupted my nap

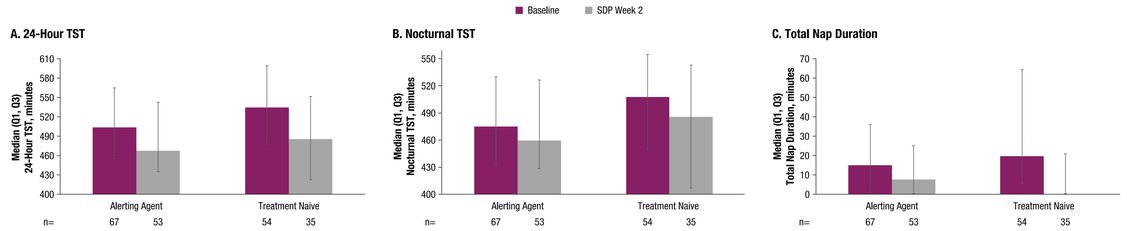
Results

Figure 2. Decreased Sleep Duration With Open-label LXB Treatment



Estimated median changes from baseline (95% CI) in the safety population, <8 h baseline 24-h TST subgroup, and ≥8 to <9 h baseline 24-h TST subgroup, respectively, were:
A. 24-Hour TST: −38 (−61 to −9) min, *P*=0.0002; −1 (−32 to 19) min, *P*=0.6772; and −42 (−69 to 28) min, *P*=0.3554.
B. Nocturnal TST: −23 (−41 to 0) min, *P*=0.0140; 0 (−24 to 19) min, *P*=0.6229; and −15 (−66 to 28) min, *P*=0.6661.
C. Total Nap Duration: −8.3 (−12.0 to −1.6) min, *P*<0.0001; −1.0 (−10.3 to 0.0) min, *P*=0.6948; and −2.5 (−12.0 to 0.0) min, *P*=0.1991.
LXB, low-sodium oxybate; Q1, first quartile; Q3, third quartile; SDP, stable-dose period; TST, total sleep time.

Figure 3. Decreased Sleep Duration With Open-label LXB Treatment by Pharmacotherapy at Study Entry



Estimated median changes from baseline (95% CI) in participants taking alerting agents at study entry and treatment-naive participants, respectively, were:
A. 24-Hour TST: −28 (−57 to 14) min, *P*=0.0261; and −61 (−100 to −33) min, *P*<0.0023.
B. Nocturnal TST: −23 (−41 to 14) min, *P*=0.1964; and −32 (−77 to 7) min, *P*=0.0233.
C. Total Nap Duration: −8.4 (−12.0 to 0.0) min, *P*=0.0158; and −11.3 (−43.4 to −2.5) min, *P*=0.0006.
LXB, low-sodium oxybate; Q1, first quartile; Q3, third quartile; SDP, stable-dose period; TST, total sleep time.

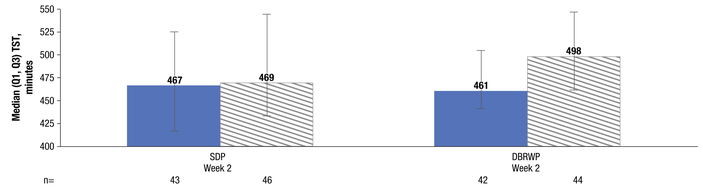
Table 2. Demographics and Baseline Disease Characteristics

Characteristic	On Baseline Idiopathic Hypersomnia Medication[a] (n=82)	Treatment Naive[b] (n=66)	Safety Population[c] (N=148)
Age, mean (SD)	40.8 (13.0)	39.4 (14.3)	40.2 (13.5)
Female, n (%)	62 (75.6)	40 (60.6)	102 (68.9)
Race, n (%)			
White	74 (90.2)	53 (80.3)	127 (85.8)
Black or African American	5 (6.1)	4 (6.1)	9 (6.1)
Other[d]	3 (3.7)	9 (13.6)	12 (8.1)
Idiopathic hypersomnia diagnosis[e], n (%)			
With long sleep	12 (14.6)	17 (25.8)	29 (19.6)
Without long sleep	70 (85.4)	49 (74.2)	119 (80.4)

[a]Includes participants who were taking an alerting agent (stimulant or wake-promoting agent) at study entry. [b]Includes participants not taking high-sodium oxybate or an alerting agent (stimulant or wake-promoting agent) at study entry. [c]Includes all participants who took ≥1 dose of study drug. [d]Includes declined to state. [e]A diagnosis of idiopathic hypersomnia with or without long sleep was determined by investigators per *International Classification of Sleep Disorders*, 2nd Edition (ICSD-2) or ICSD-3 criteria.

- A total of 4596 daily diary records were submitted by the 154 enrolled participants
- 679 daily diary records from 123 participants were excluded due to erroneous clock entries; 242 records from 73 participants had >1 error
- 3917 daily sleep diary records from 154 participants were analyzed

Figure 4. Worsening in Total Sleep Time After Randomization to Placebo



Includes participants who were taking an idiopathic hypersomnia medication (SXB and/or an alerting agent [stimulant or wake-promoting agent] at study entry) or who were treatment naive (not taking SXB or an alerting agent at study entry).
DBRWP, double-blind randomized withdrawal period; LXB, low-sodium oxybate; Q1, first quartile; Q3, third quartile; SDP, stable-dose period; SXB, high-sodium oxybate; TST, total sleep time.

- Common treatment-emergent adverse events (reported by ≥10% of total participants across all study periods, excluding placebo data) were nausea (22.1%), headache (17.5%), dizziness (12.3%), anxiety (11.0%), and vomiting (11.0%)

Conclusions

- In adults with idiopathic hypersomnia treated with low-sodium oxybate, a reduction in 24-hour total sleep time, nocturnal sleep time, and total nap duration was observed during the open-label treatment phase in both baseline treatment groups and in participants with higher baseline 24-hour total sleep time
  - The estimated median decrease in 24-hour total sleep time was 115 minutes in participants with baseline 24-hour total sleep time of ≥9 hours
- In this controlled, randomized study, 24-hour total sleep time increased (worsened) when participants switched to placebo but remained stable in participants who continued LXB treatment

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** Trotti LM, Arnulf I. *Neurotherapeutics*. 2021;18:20-31. **3.** Billiard M, Sonka K. *Sleep Med Rev*. 2016;29:23-33. **4.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **5.** Szarfman A, et al. *N Engl J Med*. 1995;333(19):1291. **6.** US Food and Drug Administration. Clinical Review for Binosto, NDA 202344. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **7.** 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. Available at: https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescriptiondrug. **8.** Dauvilliers Y, et al. *Lancet Neurol*. 2022;21:53-65.

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