325

Effectiveness and Safety of Low-Sodium Oxybate by Patient-Reported Long Sleep Need in DUET Study Participants With Idiopathic Hypersomnia

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Objective

- To evaluate effectiveness and safety outcomes of low-sodium oxybate (LXB) treatment in subcohorts of DUET participants with idiopathic hypersomnia stratified by self-reported ideal nighttime sleep duration (with [>9 hours] or without [≤9 hours] long sleep need)

Conclusions

- Participants taking LXB, both with long sleep need (>9 hours) and without long sleep need (≤9 hours), showed improvements across multiple idiopathic hypersomnia outcomes and symptoms including reduced total sleep time, reduced excessive daytime sleepiness and improved daytime functioning
- Participants taking LXB reported improved daytime sleepiness despite having decreased objective total sleep time, which is a meaningful finding due to the common complaint of prolonged, nonrestorative sleep among people with idiopathic hypersomnia
- Limitations include that effectiveness analyses were not powered for formal comparisons and were based on the completer analysis set of participants who reached a stable LXB dosage (which may not represent the experience of all individuals starting LXB treatment)
- The safety profiles in both subcohorts were generally similar to that of the overall idiopathic hypersomnia cohort

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Plante DL, et al. *CNS Drugs*. Published online March 14, 2026. doi.org/10.1007/s40263-025-01262-9. **3.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition*, Text Revision. Darien, IL: American Academy of Sleep Medicine; 2023. **4.** Dauvilliers Y, et al. *Neurology.* 2019;92(15):e1754-e1762. **5.** Rassu AL, et al. *J Clin Sleep Med.* 2022;18(2):617-629. **6.** Johns MW. *Sleep.* 1991;14(6):540-545. **7.** Maski K, et al. *J Clin Sleep Med*. 2021;17(9):1895-1945.

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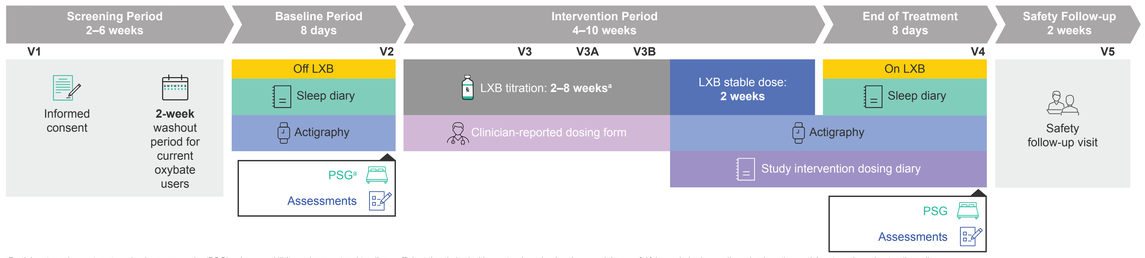
Introduction

- Low-sodium oxybate (LXB; Xywav®), the only FDA-approved treatment for idiopathic hypersomnia in adults,[1] was evaluated for effectiveness and safety in DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment), a phase 4, prospective, single-arm, open-label study (NCT05875974)[2]
- Idiopathic hypersomnia is often seen as a heterogeneous disorder, with some patients showing long sleep time[3]; however, daily demands may restrict patients' abilities to engage in long sleep time
- The Idiopathic Hypersomnia Severity Scale (IHSS)[4] is a validated tool used in clinical and research settings to quantify symptoms of idiopathic hypersomnia
- The present analysis used item 1 of the IHSS to probe treatment differences in DUET participants expressing long sleep need (LSN) based on self-reported ideal sleep length

Methods

- DUET enrolled adults 18 to 75 years of age with a primary diagnosis of idiopathic hypersomnia and comprised screening, baseline (BL), LXB dose titration/optimization, stable-dose (SDP), end-of-treatment (EOT), and safety follow-up periods (**Figure 1**)
- Additional study methodology details can be found in the Supplement, accessed via the QR code

Figure 1. DUET Study Design



[a]Participants underwent nocturnal polysomnography (PSG) using an ad libitum sleep protocol to allow sufficient time in bed with a natural awakening time; a minimum of 10 hours in bed was allowed unless the participant awakened naturally earlier.
Figure adapted from Nichols DA, et al. *Neural Ther.* 2025;14:1705–727. http://creativecommons.org/licenses/by-nc/4.0/.
DUET, **D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment; LXB, low-sodium oxybate; PSG, polysomnography; V, visit.

- Participants were divided into subcohorts with (>9 hours) or without LSN (≤9 hours) based on their responses to IHSS Item 1 at BL: "*What for you is the ideal duration of nighttime sleep (at the weekend or on holiday, for example)?*" (Response options: "11 hours or more," "more than 9 hours and less than 11 hours," "between 7 hours and 9 hours," "less than 7 hours")
- Effectiveness outcomes evaluated by subcohort were: Epworth Sleepiness Scale (ESS) score, IHSS total score and the IHSS Daytime Functioning Component score (comprised of IHSS items 5, 9, 10, 11, 12, 13, and 14[5]), polysomnographic total sleep time (TST), Patient Global Impression of Severity (PGI-S), and Patient Global Impression of Change (PGI-C)
- Safety assessment was based on incidence and severity of treatment-emergent adverse events (TEAEs) reported in each subcohort

Results

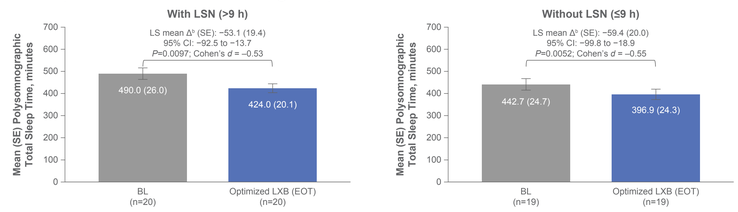
Table 1. Demographics and Baseline Characteristics in Participants With or Without Long Sleep Need[a]

Characteristic	With LSN (>9 h) n=24	Without LSN (≤9 h) n=21	Total Idiopathic Hypersomnia Cohort N=46[b]
Mean (SD) age, years	36.8 (11.1)	38.6 (12.1)	38.1 (11.8)
Mean (SD) body mass index, kg/m²	28.3 (7.4)	28.6 (5.4)	28.5 (6.4)
Oxybate type at study entry, n (%)			
Naive[d]	19 (79.2)	18 (85.7)	37 (80.4)
Low-sodium oxybate	5 (20.8)	3 (14.3)	9 (19.6)
Sex at birth, n (%)			
Male	24 (100)	8 (38.1)	9 (19.6)
Female		13 (61.9)	37 (80.4)
Race, n (%)			
White	1 (4.2)	1 (4.8)	1 (2.2)
Black or African American	1 (4.2)	1 (4.8)	2 (4.3)
Asian			1 (2.2)
Native Hawaiian or Other Pacific Islander			
Multiple[c]	22 (91.7)	16 (76.2)	39 (84.8)
		3 (14.3)	3 (6.5)
Ethnicity, n (%)			
Hispanic or Latino	8 (33.3)	2 (9.5)	10 (21.7)
Not Hispanic or Latino	16 (66.7)	18 (85.7)	35 (76.1)
Concomitant alerting agents[e], n (%)			
Yes	8 (33.3)	10 (47.6)	19 (41.3)
No	16 (66.7)	11 (52.4)	27 (58.7)

[a]Safety analysis set; of the 46 enrolled participants with idiopathic hypersomnia, 45 had BL IHSS data (24 reported LSN [>9 h] and 21 reported no LSN [≤9 h]). [b]The participant who did not complete the IHSS at BL could not be included in the subcohorts but was counted in the total idiopathic hypersomnia cohort. [c]Participant reported more than 1 race. [d]No oxybate use within 2 weeks before entering the study. [e]Alerting agents were defined as stimulants or wake-promoting agents; participants must have taken the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study.
BL, baseline; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; LXB, low-sodium oxybate; SD, standard deviation.

- 100% of participants with LSN were female
- Dosage details can be found in the supplemental material, accessed via the QR code

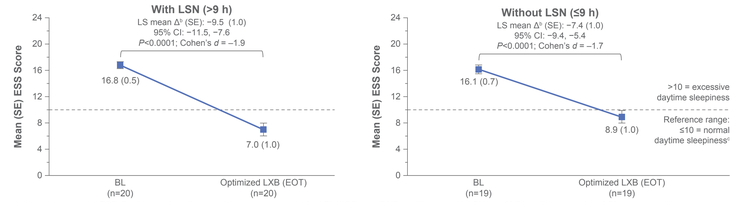
Figure 2. Objective Total Sleep Time Decreased With Optimized LXB Treatment in Participants With or Without Long Sleep Need[a]



[a]Participants from the completer analysis set who had BL IHSS data (20/24 participants with LSN and 19/21 participants without LSN completed the study). [b]Difference between EOT and BL.
BL, baseline; CI, confidence interval; EOT, end of treatment; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least squares; LSN, long sleep need; LXB, low-sodium oxybate; SE, standard error.

- In both subcohorts, total sleep time decreased by about 1 hour from BL to EOT

Figure 3. Daytime Sleepiness Improved With Optimized LXB Treatment in Participants With or Without Long Sleep Need[a]



[a]Analysis based on the ESS. Participants from the completer analysis set who had BL IHSS data (20/24 participants with LSN and 19/21 participants without LSN completed the study). [b]Difference between EOT and BL. [c]Established categories consider scores up to 10 normal.[6] The MCID for ESS was defined as 2 points according to an AASM systematic review and meta-analysis.[7] *P* values are nominal.
AASM, American Academy of Sleep Medicine; ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least squares; LSN, long sleep need; LXB, low-sodium oxybate; MCID, minimal clinically important difference; SE, standard error.

- Mean ESS scores for both subcohorts at EOT were within the range of normal daytime sleepiness, with the change from BL exceeding the minimal clinically important difference (2-point change)[7]

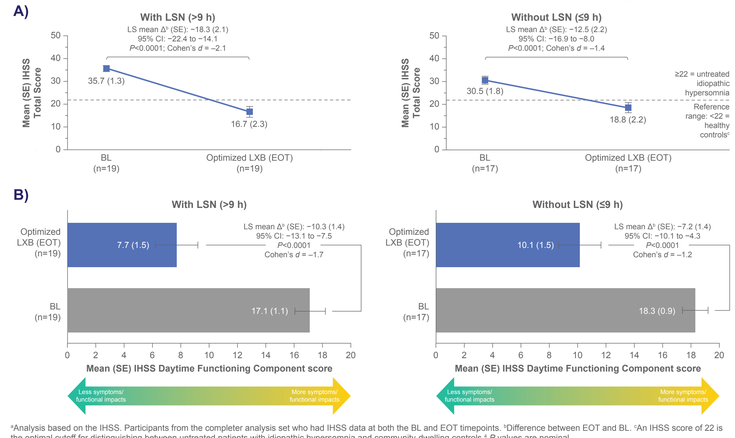
Table 2. Summary of Treatment-Emergent Adverse Events in Participants With or Without Long Sleep Need[a]

Participants, n (%)	With LSN (>9 h) n=24	Without LSN (≤9 h) n=21	Total Idiopathic Hypersomnia Cohort N=46
With ≥1 TEAE	19 (79.2)	14 (66.7)	34 (73.9)
With ≥1 serious TEAE	0	1 (4.8)	1 (2.2)
With ≥1 TEAE related to treatment	19 (79.2)	11 (52.4)	30 (65.2)
With ≥1 TEAE leading to discontinuation	1 (4.2)	0	1 (2.2)
TEAEs occurring in ≥5% of participants			
Nausea	7 (29.2)	2 (9.5)	9 (19.6)
Dizziness	6 (25.0)	2 (9.5)	8 (17.4)
Headache	4 (16.7)	4 (19.0)	8 (17.4)
Vomiting	4 (16.7)	0	5 (10.9)
Middle insomnia	1 (4.2)	3 (14.3)	4 (8.7)
Anxiety	2 (8.3)	1 (4.8)	3 (6.5)
Decreased appetite	1 (4.2)	2 (9.5)	3 (6.5)
Enuresis	2 (8.3)	1 (4.8)	3 (6.5)
Somnolence	2 (8.3)	1 (4.8)	3 (6.5)
Bruxism	0	2 (9.5)	2 (4.3)
Cough	0	2 (9.5)	2 (4.3)
Hyperhidrosis	2 (8.3)	0	2 (4.3)
Nasal congestion	0	2 (9.5)	2 (4.3)
	Lowest Highest	Lowest Highest	Lowest Highest

[a]Safety analysis set; of 46 enrolled participants with idiopathic hypersomnia, 45 had BL IHSS data (24 reported LSN [>9 h] and 21 reported no LSN [≤9 h]).
BL, baseline; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; TEAE, treatment-emergent adverse event.

- TEAEs were reported in 79.2% of participants with LSN and 66.7% of participants without LSN
- Most TEAEs in participants with or without LSN, respectively, were mild (45.8% and 42.9%) or moderate (33.3% and 23.8%) in severity; 1 TEAE of hypoxia (concurrent with influenza) in the subcohort without LSN was serious and considered unrelated to study drug and resolved

Figure 4. Idiopathic Hypersomnia Overall Symptoms (A) and Daytime Functioning (B) Improved With Optimized LXB Treatment in Participants With or Without Long Sleep Need[a]

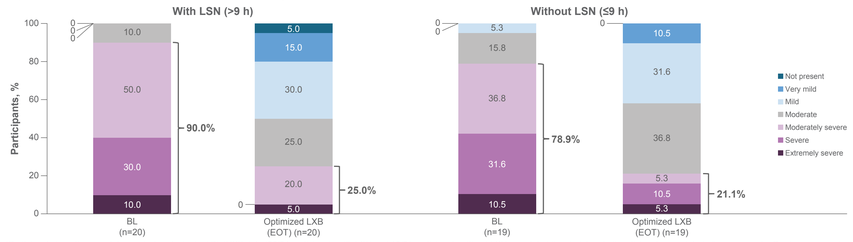


[a]Analysis based on the IHSS. Participants from the completer analysis set who had IHSS data at both the BL and EOT timepoints. [b]Difference between EOT and BL. [c]An IHSS score of 22 is the optimal cutoff for distinguishing between untreated patients with idiopathic hypersomnia and community-dwelling controls.[4] *P* values are nominal.
BL, baseline; CI, confidence interval; EOT, end of treatment; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least squares; LSN, long sleep need; LXB, low-sodium oxybate; SE, standard error.

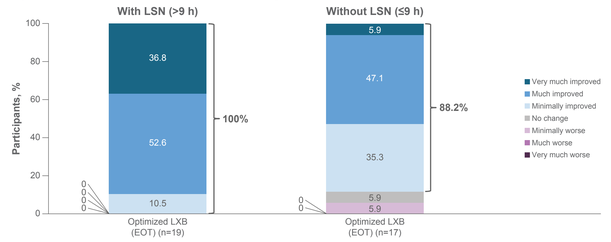
- Mean IHSS total scores for both subcohorts at EOT were in the established range of healthy controls[4]; the change from BL to EOT was clinically meaningful for both subcohorts, exceeding the minimal clinically important difference (4-point change)[5]
- The IHSS Daytime Functioning Component Score decreased in both subcohorts, indicating an improvement in daytime symptoms and functioning

Figure 5. Fewer Participants Reported Overall Disease as "Severe" With LXB Treatment[a] (A); All Participants With Long Sleep Need, and Most Without Long Sleep Need, Reported Improved Overall Disease With LXB Treatment[a] (B)

A) Patient Global Impression of Severity



B) Patient Global Impression of Change



[a]Participants from the completer analysis set who had BL IHSS data (20/24 participants with LSN and 19/21 participants without LSN completed the study); not all participants completed all assessments. *P* values are nominal.
BL, baseline; EOT, end of treatment; h, hour; IHSS, Idiopathic Hypersomnia Severity Scale; LSN, long sleep need; LXB, low-sodium oxybate.

325

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Supplemental Material

Supplemental Figure S1. Key Enrollment Eligibility Criteria: DUET Idiopathic Hypersomnia Cohort

Inclusion Criteria

- Adults 18–75 years of age with a primary diagnosis of idiopathic hypersomnia (ICSD-3)
- ESS score >10[a]
- Concomitant stable use of alerting agents allowed[b]

Exclusion Criteria

- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[c]
- History/presence of other untreated, inadequately treated, or unstable disorder or condition (eg, sleep, medical, behavioral/ psychiatric, neurologic)[d]
- Medication(s) contraindicated, with known drug-drug interaction, or similar EEG effects as LXB or known to have clinically significant CNS sedating effects

[a]At screening visit 1 or, if taking an oxybate medication at screening, at visit 2. [b]Alerting agents were defined as stimulants or wake-promoting agents; participants must have taken the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study. [c]Hypopnea definition included a ≥4% desaturation as per Rule 1B of *The AASM Manual for the Scoring of Sleep and Associated Events*, as assessed during the baseline PSG visit. [d]Disorder or condition that might affect the participant's safety and/or interfere with the conduct of the study, in the opinion of the investigator.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; CNS, central nervous system; DUET, **D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment; EEG, electroencephalogram; ESS, Epworth Sleepiness Scale; ICSD-3, *International Classification of Sleep Disorders – Third Edition*; LXB, low-sodium oxybate; PSG, polysomnography.

- The safety analysis set includes all enrolled participants who took their prescribed LXB regimen for ≥1 night after the BL period (evaluated for demographics/BL characteristics, dosing, TEAEs); the completer analysis set includes all enrolled participants who took their prescribed LXB regimen for ≥1 night after the BL period and completed the SDP and PSG EOT visit (evaluated for ESS, IHSS, TST, PGI-S, and PGI-C)

Statistical Analyses

- Least squares mean change from baseline to EOT, SE, 95% CI, and *P* values were generated using an analysis of covariance model adjusted for the BL value. *P* values are not controlled for multiplicity and are nominal
- Cohen's *d* effect sizes were generated for the change from BL to EOT for each subcohort (with/without LSN) for total sleep time, IHSS total score, and IHSS daytime functioning component score

Supplemental Table S1. Mean Nightly LXB Dosage During Stable-Dose Period Was Comparable in Participants With or Without LSN[a]

Participants, n (%)	With LSN (>9 h) n=21	Without LSN (≤9 h) n=19	Total Idiopathic Hypersomnia Cohort n=40
Total once-nightly dosage, g/night, n	8	7	15
Mean (SD)	4.8 (1.0)	4.8 (1.3)	4.8 (1.1)
Total twice-nightly dosage, g/night, n	13	12	25
Mean (SD)	7.8 (1.1)	7.4 (1.4)	7.6 (1.2)
First nightly LXB dose	3.9 (0.5)	4.1 (1.0)	4.0 (0.8)
Second nightly LXB dose	3.9 (0.7)	3.4 (0.9)	3.6 (0.8)

[a]Includes participants from the safety analysis set who reached the stable-dose period.
h, hour; LSN, long sleep need; LXB, low-sodium oxybate; SD, standard deviation.

- Mean (standard deviation) nightly LXB dosage during the SDP was comparable between subcohorts
  - Total once-nightly dosage: 4.8 (1.0) g/night for participants with LSN and 4.8 (1.3) g/night for those without LSN
  - Total twice-nightly dosage: 7.8 (1.1) g/night for participants with LSN and 7.4 (1.4) g/night for those without LSN

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