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Sleep Architecture With Low-Sodium Oxybate Treatment in Idiopathic Hypersomnia: Results From the DUET Study

DUET STUDY 407

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Introduction

- Individuals with idiopathic hypersomnia often experience nonrestorative nighttime sleep;[1-4] however, relatively few polysomnography (PSG) studies have been performed, and findings are mixed
  - Meta-analysis of PSG has suggested that individuals with idiopathic hypersomnia have longer sleep times, lower proportions of N3 sleep, and greater proportions of rapid eye movement (REM) sleep compared with healthy controls[5]
  - Other reported indicators of sleep instability in idiopathic hypersomnia include increased arousals[6-8]
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration for the treatment of idiopathic hypersomnia in adults and the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age or older with narcolepsy[9-12]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, multicenter, single-arm, multiple-cohort, open-label study (NCT05875974) evaluating the effectiveness of LXB in treating daytime and nighttime symptoms, including PSG-based sleep architecture, in participants with idiopathic hypersomnia or narcolepsy (type 1 or 2)
  - Top-line results from the DUET study for the narcolepsy and idiopathic hypersomnia cohorts are presented in **Poster 393** and **Poster 413**, respectively
  - Subjective sleep quality results for the narcolepsy and idiopathic hypersomnia cohorts are presented in **Poster 422** and **Poster 414**, respectively

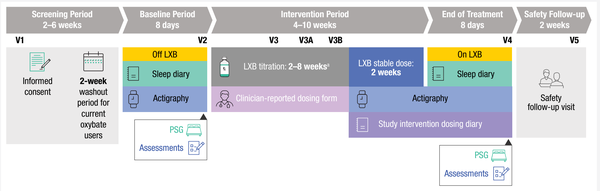
Objective

- To evaluate the effect of LXB on PSG-based sleep architecture in the cohort of individuals with idiopathic hypersomnia

Methods

- DUET included a screening period (with a washout for current oxybate users), a baseline (BL) period, a titration period (participants began LXB treatment with individualized dosing adjustments to achieve their optimal dose), a stable-dose period (SDP; at the optimal LXB dose), an end-of-treatment (EOT) period, and a safety follow-up
  - Participants could be treated with a once- or twice-nightly LXB based on the investigator's discretion in the idiopathic hypersomnia cohort (per US prescribing label)[9]
- At BL and EOT, participants underwent nocturnal PSGs using an *ad libitum* protocol to allow sufficient time in bed with a natural final awakening
  - PSG recordings were obtained according to standard protocol/montage and were centrally scored
- PSG-measured outcomes in the IH cohort were exploratory endpoints
  - Least squares mean differences (95% confidence interval) at the EOT visit were estimated using a mixed model with repeated measures (analysis of covariance) adjusted for the BL value
  - *P* values for exploratory endpoints were not controlled for multiplicity; therefore, *P* values are considered nominal
- The safety analysis set includes all participants who enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period; the completer analysis set includes all participants who enrolled in the study, took their prescribed LXB regimen for ≥1 night after the BL period, completed the SDP, and completed the PSG EOT visit

Figure 1. Study Design



***Ad libitum* PSG protocol**
- Bedtime was determined by habitual bedtime (same bedtime used for baseline and EOT visits)[b]
- PSG was scheduled to allow a minimum of 10 hours time in bed, unless the participant naturally awakened earlier
- For logistical reasons, wake time must have occurred by noon (±15 minutes to avoid awakening from deep [stage N3] sleep)

[a]Weekly titration visits were by teleconference. Visit 3 occurred on titration day 14. Titration could take between 2 and 8 weeks. Additional in-clinic visits were scheduled for day 35 (visit 3A) and day 56 (visit 3B), as needed. Investigator could optimize participant dosage and move participant to SDP at visit 3, 3A, or 3B, but not during intervening weekly teleconferences. [b]For BL PSG, when participants were not taking LXB, only an initial lights off and a final lights on were recorded (no awakening by investigator). For EOT PSG, the first LXB dose was taken immediately before lights off, the participant was awakened 3 hours 58 minutes post-lights off, and the second LXB dose (if applicable) was taken prior to a second lights off at 4 hours 0 minutes after the initial lights off. Participants took each dose of LXB while in bed, laid down immediately after dosing, and remained in bed following each dose.
EOT, end of treatment; LXB, low-sodium oxybate; N3, non-REM stage 3; PSG, polysomnography; SDP, stable-dose period; V, visit.

Figure 2. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
- 18–75 years of age with primary diagnosis of idiopathic hypersomnia (per ICSD-3 criteria)
  - Individuals with and without long sleep time were included[b]
- ESS score >10[b]
- Participants were allowed to continue taking concomitant alerting agents (stimulants or wake-promoting agents), but had to have been taking the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study period

Key Exclusion Criteria
- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[c]
- History/presence of other untreated/inadequately treated sleep disorder or unstable/clinically significant medical condition, behavioral/psychiatric disorder, neurologic disorder, or surgical history that might affect the participant's safety or interfere with study conduct

[a]Analyses are performed for the complete idiopathic hypersomnia cohort, with no distinction made between those with and without long sleep time. [b]At screening visit 1 or at visit 2 if currently taking an oxybate medication, after the washout period. [c]Hypopnea definition included ≥4% desaturation per *The AASM Manual for the Scoring of Sleep and Associated Events*[11], as assessed during baseline PSG visit.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; ICSD-3, *International Classification of Sleep Disorders – Third Edition*; PSG, polysomnography.

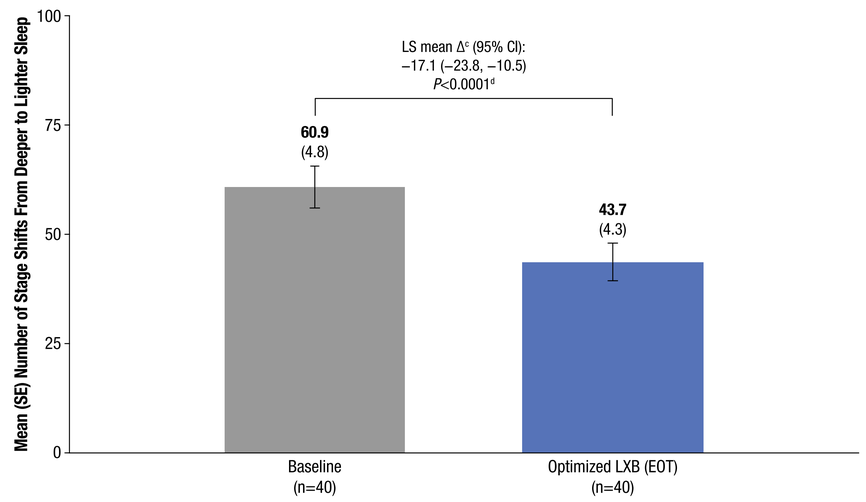
Results

Table 1. Demographics and Baseline Characteristics of Participants With Idiopathic Hypersomnia[a,b]

Characteristic	Total (N=46)
Age (years), mean (SD)	38.1 (11.8)
Sex at birth, n (%)	
Male	9 (19.6)
Female	37 (80.4)
Race, n (%)	
White	39 (84.8)
Black or African American	3 (6.5)
American Indian or Alaska Native	0
Asian	2 (4.3)
Native Hawaiian or other Pacific Islander	1 (2.2)
Multiple[c]	1 (2.2)
Body mass index (kg/m²), mean (SD)	28.5 (6.4)
Oxybate type at study entry, n (%)	
Naive[d]	37 (80.4)
Low-sodium oxybate	9 (19.6)
Sodium oxybate	0
Once-nightly sodium oxybate	0
Concomitant alerting agent , n (%)[e,f,g]	19 (41.3)

[a]Safety analysis set. [b]For additional demographic information, including concomitant alerting agent use, please see **Poster 413**. [c]Participant reported >1 race. [d]No oxybate use within 2 weeks of entering study. [e]Participants could have been taking multiple alerting medications. [f]These agents could have been prescribed for excessive sleepiness, idiopathic hypersomnia, and/or another condition. [g]Concomitant medications had a stop date on or after the date of the first dose of the study intervention or were ongoing.
SD, standard deviation.

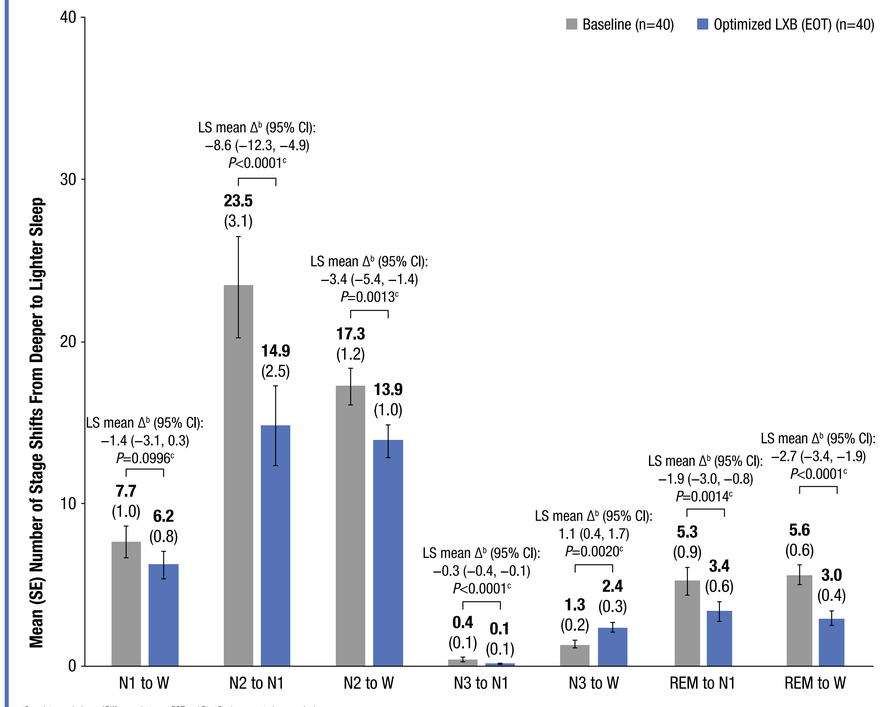
Figure 3. Total Number of Shifts From Deeper to Lighter Sleep Stages Decreased From Baseline to End of Treatment[a,b]



[a]Completer analysis set. [b]Includes total sleep stage shifts from N1/N2/N3/REM to W and N2/N3/REM to N1. [c]Difference between EOT and BL. [d]*P* values reported are nominal.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1/2/3, non-REM stage 1/2/3; PSG, polysomnography; REM, rapid eye movement; SE, standard error; W, wake.

- **Total shifts index** (total shifts/h of total sleep time):
  - Mean (SE): 6.7 (0.5) at BL and 5.3 (0.5) at EOT; LS mean change (95% CI) from baseline: −1.5 (−2.2, −0.8); *P*=0.0001

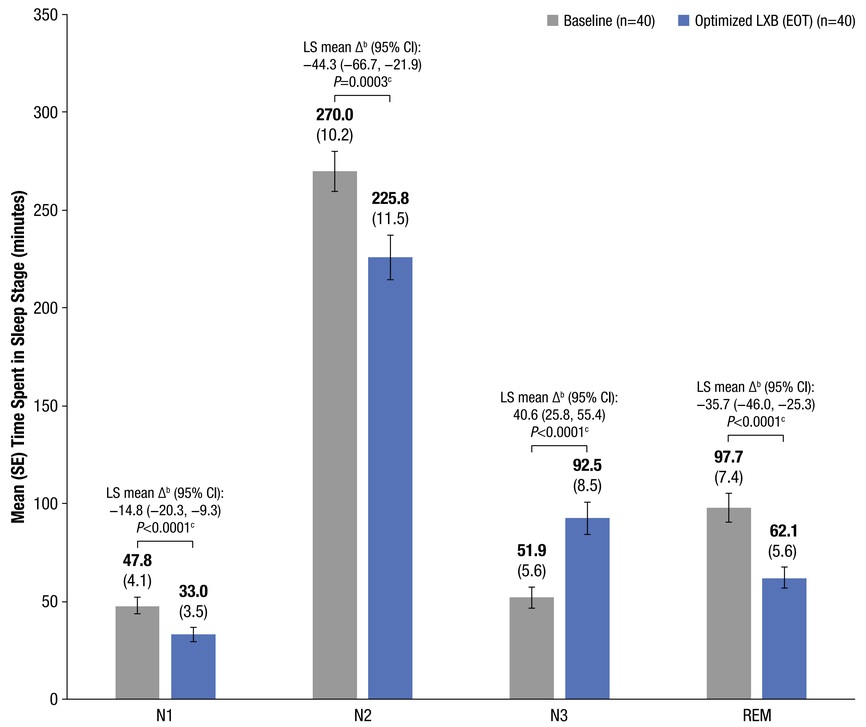
Figure 4. Shifts From Deeper to Lighter Sleep Stages Generally Decreased From Baseline to End of Treatment[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1/2/3, non-REM stage 1/2/3; REM, rapid eye movement; SE, standard error; W, wake.

- Reductions in the mean number of shifts from N2 to N1, N2 to W, N3 to N1, REM to N1, and REM to W were observed; however, there were increases in the mean number of shifts from N3 to W

Figure 5. Time (Minutes of TST) Spent in N1, N2, and REM Decreased While Time Spent in N3 Increased From Baseline to End of Treatment[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1/2/3, non-REM stage 1/2/3; REM, rapid eye movement; SE, standard error.

Table 2. Other PSG-Measured Sleep Parameters[a]

Parameter	BL, mean (SE) (n=40)	Optimized LXB (EOT), mean (SE) (n=40)	LS mean Δ[b] (95% CI)	*P* value[c]
Time in bed (min)	562.7 (16.7)	511.3 (12.5)	−51.5 (−73.3, −29.7)	<0.0001
Total sleep time (min)	467.5 (17.7)	413.4 (15.5)	−54.1 (−81.3, −26.9)	0.0003
Sleep efficiency (%)	82.7 (1.7)	80.6 (1.9)	−2.1 (−5.9, 1.7)	0.2785
Sleep onset latency (min)	14.5 (2.6)	18.9 (2.2)	4.4 (−0.2, 8.9)	0.0576
REM latency (min)	127.0 (12.2)	133.7 (14.8)	8.4 (−20.3, 37.1)	0.5566

[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal.
CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; min, minute; PSG, polysomnography; REM, rapid eye movement; SE, standard error.

- Time in bed and total sleep time decreased with LXB treatment
- Sleep efficiency, sleep onset latency, and REM latency did not appear to change with LXB treatment

Table 3. Percentage of Time (% of TST) Spent in N1, N2, and REM Decreased While Time in N3 Increased From Baseline to End of Treatment[a]

Sleep stage (% of TST)	BL, mean (SE) (n=40)	Optimized LXB (EOT), mean (SE) (n=40)	LS mean Δ[b] (95% CI)	*P* value[c]
N1	10.3 (0.8)	8.0 (0.8)	−2.3 (−3.7, −0.9)	0.0017
N2	58.5 (1.4)	54.2 (2.0)	−4.3 (−8.1, −0.5)	0.0286
N3	11.2 (1.3)	22.8 (2.2)	11.6 (7.9, 15.3)	<0.0001
REM	20.0 (1.2)	15.0 (1.2)	−5.0 (−7.4, −2.7)	0.0001

[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1/2/3, non-REM stage 1/2/3; REM, rapid eye movement; SE, standard error; TST, total sleep time.

Table 4. Treatment-Emergent Adverse Events[a,b]

Participants, n (%)	Total (N=46)
With ≥1 TEAE	34 (73.9)
With ≥1 TEAE related to treatment	30 (65.2)
TEAEs occurring in ≥5% of participants	
Nausea	9 (19.6)
Dizziness	8 (17.4)
Headache	8 (17.4)
Vomiting	5 (10.9)
Middle insomnia	4 (8.7)
Anxiety	3 (6.5)
Decreased appetite	3 (6.5)
Enuresis	3 (6.5)
Somnolence	3 (6.5)

[a]Safety analysis set. [b]For additional safety information, please see **Poster 413**.
TEAE, treatment-emergent adverse event.

- One (2.2%) participant had a serious treatment-emergent adverse event (hypoxia [concurrent with influenza] that was of moderate severity, determined to be unrelated to study drug in the opinion of the investigator, and resolved)

Conclusions

- Using an *ad libitum* PSG protocol, participants with idiopathic hypersomnia taking open-label LXB experienced reduced total sleep time and time in bed, with group-wise improvements in daytime sleepiness (see **Poster 413**)
  - Changes in sleep architecture included increased N3 sleep and reduced REM sleep, which suggests potential correction of underlying differences in sleep architecture between idiopathic hypersomnia and controls that have been previously described in meta-analysis[5]
  - Further, these participants demonstrated decreases in N1 sleep and fewer transitions from deeper to lighter stages of sleep with LXB, similar to changes observed in individuals with narcolepsy (see **Poster 424**)
- Limitations of the DUET study include 1) the open-label design and lack of a control group limit ability to attribute findings solely to LXB and 2) analyses 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
- These findings represent the first evaluation of LXB treatment on sleep architecture in individuals with idiopathic hypersomnia, substantially expanding our understanding of baseline and LXB-treated sleep in idiopathic hypersomnia

References: 1. Vernet C, et al. *J Sleep Res.* 2010;19:525-34. **2.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **3.** Ali M, et al. *J Clin Sleep Med.* 2009;5:562-8. **4.** Trotti LM, et al. *Sleep Med.* 2020;75:343-9. **5.** Plante DT. *Sleep Med.* 2018;45:17-24. **6.** Pizza F, et al. *J Sleep Res.* 2013;22:185-96. **7.** Maski KP, et al. *Sleep.* 2021;44:zsab021. **8.** Sforza E, et al. *Sleep Med.* 2016;24:131-6. **9.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2023. **10.** Szarfman A, et al. *N Engl J Med.* 1995;333:1291. **11.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **12.** 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-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **13.** Berry RB, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 3. Darien, IL: American Academy of Sleep Medicine; 2023.

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Supplemental Statistical Methods

- Formal hypothesis testing was conducted in accordance with the statistical analysis plan using the completer analysis set for the endpoints Epworth Sleepiness Scale (ESS) score (decrease from baseline [BL]) and Idiopathic Hypersomnia Severity Scale (IHSS) total score (decrease from BL). Additional study details can be found on **Poster 413**
- Decreases from BL for ESS and IHSS total scores were estimated using an analysis of covariance (ANCOVA) model adjusted for the BL value. The parameter of interest for each endpoint, the least-squares mean difference at the end-of-treatment visit, was compared against a null hypothesis value of 0
- Other reported endpoints were not controlled for multiplicity. Hypothesis tests with 2-sided $P<0.05$ in the expected direction were considered statistically significant. If any ordered endpoint failed to reject the null hypothesis, subsequent hypothesis tests were considered nominal. Hypothesis tests for endpoints not included in the sequential testing procedure were considered nominal
- The shift index was calculated using the total shift parameter and divided by the sleep period to yield an index per hour of sleep

Centralized Polysomnography Scoring Definitions:

- **Epoch:** a standard 30-second duration of the sleep recording that is assigned a sleep stage value
- **Stage W:** corresponds to the waking state ranging from full alertness through the early stages of drowsiness; characterized by alpha activity in the electroencephalogram (EEG): trains of sinusoidal 8 to 13 Hz activity recorded over the occipital region with eye closure, attenuating with eye opening; any epoch between lights off and lights on during which a participant is out of bed is scored as Stage W
- **Stage N1:** a relatively low amplitude, mixed frequency (LAMF) EEG with a majority of activity in the 4 to 7 Hz range; vertex sharp waves may occur and are distinguishable from background EEG activity, maximal over the central region; slow eye movements typically are present; rapid eye movements are absent; tonic electromyographic (EMG) levels are usually below those of relaxed wakefulness
- **Stage N2:** the presence of sleep spindles and/or K complexes (maximal over the central region) and the absence of sufficient high-amplitude, slow activity to define the presence of N3 sleep stage
- **Stage N3:** an EEG (epoch) with ≥20% of an epoch consisting of slow, high amplitude waveforms of 0.5 to 2 Hz and peak-to-peak amplitude of >75 mV
- **Stage R:** rapid eye movement (REM) sleep is defined by the concomitant appearance of LAMF EEG activity and episodic REMs; sawtooth waves (2–6 Hz waves maximal over the central region) may be present; chin EMG activity is typically low, and REM sleep is not scored in the presence of relatively elevated tonic mental-submental EMG activity
- **Awakening:** two consecutive epochs of wake
- **Latency to Onset of Persistent Sleep:** reported in minutes, defined as latency from lights off to the first epoch of 20 consecutive epochs of non-wake

More information on the DUET Study can be found in the following posters:

- Top-line results from the DUET study for narcolepsy and idiopathic hypersomnia cohorts presented in **Poster 393** and **Poster 413**, respectively
- Subjective sleep quality results for narcolepsy and idiopathic hypersomnia cohorts presented in **Poster 422** and **Poster 414**, respectively
- Sleep architecture for the narcolepsy cohort presented in **Poster 424**
- PSG arousals for the idiopathic hypersomnia cohort presented in **Poster 556**
- Effectiveness and safety of LXB dosages >9 g/night in narcolepsy in **Poster 558**