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

DUET STUDY 407

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Introduction

- Individuals with narcolepsy experience disrupted nighttime sleep (DNS), defined as frequent awakenings/arousals, poor sleep quality, and frequent shifts to lighter stages of sleep (N1 or wake)[1,2]
  - Together with cataplexy and excessive daytime sleepiness, DNS is 1 of the top 3 symptoms with the most significant negative effect on quality of life, including daytime functioning[2]
- Literature to date has shown that sodium oxybate (Xyrem®) improves measures of DNS and sleep architecture in people with narcolepsy[3]
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration for the treatment of idiopathic hypersomnia in adults and for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age or older with narcolepsy;[4-7] sleep architecture had not previously been evaluated in people with narcolepsy treated with nightly LXB
- 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 polysomnography (PSG)-based sleep architecture, in participants with narcolepsy (type 1 [NT1] or 2 [NT2]) or idiopathic hypersomnia

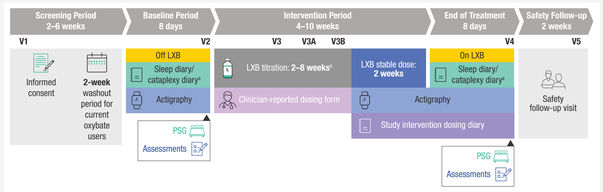
Objective

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

Methods

- DUET included a screening period (with a washout period 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 optimal LXB dose), an end-of-treatment (EOT) period, and a safety follow-up
  - All participants with narcolepsy took LXB twice nightly (per the US prescribing label)[4]
- 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
- Key secondary efficacy endpoints included total stage shifts from deeper to lighter stages of sleep (N1/N2/N3/rapid eye movement [REM] to wake and N2/N3/REM to N1) and duration of N3 sleep; other PSG-measured outcomes were exploratory
  - Least squares (LS) mean differences (95% confidence interval [CI]) at the EOT visit were estimated using a mixed model with repeated measures (analysis of covariance) adjusted for the BL value
  - *P* values for key secondary endpoints were controlled for multiplicity with sequential testing; all other *P* values were not adjusted for multiple comparisons and 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)[c]
- 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]Cataplexy diary in narcolepsy type 1 only. [b]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. [c]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 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.
BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate; N3, non-rapid eye movement stage 3; PSG, polysomnography; V, visit.

Figure 2. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
- 18–75 years of age with primary diagnosis of NT1 or NT2 (per ICSD-3 or DSM-5 criteria)
- ESS score >10[a]
- Participants were allowed to continue taking concomitant anticataplectics or alerting 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

Key Exclusion Criteria
- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[b]
- 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]At screening visit 1 or at visit 2 if taking an oxybate medication, after the washout period. [b]Hypopnea definition included a ≥4% desaturation per *The AASM Manual for the Scoring of Sleep and Associated Events*;[3] as assessed during baseline PSG visit.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ESS, Epworth Sleepiness Scale; ICSD-3, *International Classification of Sleep Disorders – Third Edition*; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography.

Results

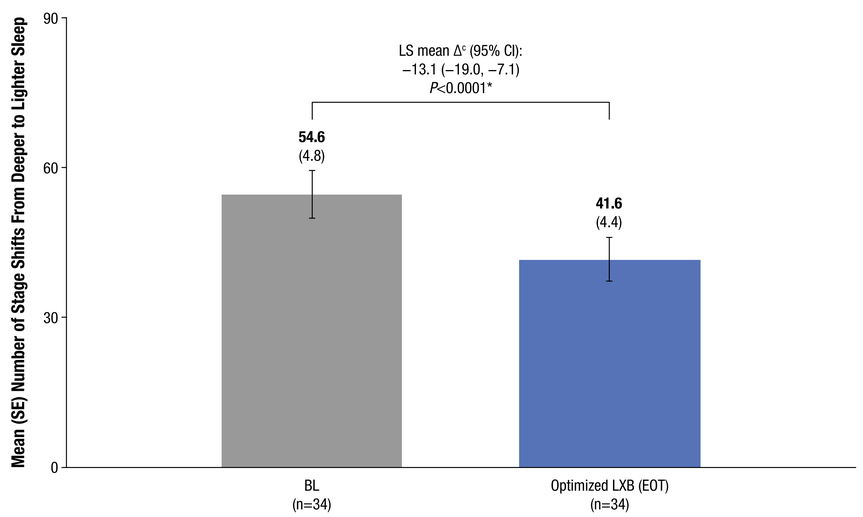
Table 1. Demographics and Baseline Characteristics of Participants With Narcolepsy[a,b]

Characteristic	Total (N=55)
Age (years), mean (SD)	33.4 (12.9)
Sex at birth, n (%)	
Male	15 (27.3)
Female	40 (72.7)
Race, n (%)	
White	44 (80.0)
Black or African American	7 (12.7)
American Indian or Alaska Native	0
Asian	2 (3.6)
Native Hawaiian or other Pacific Islander	0
Multiple[c]	1 (1.8)
Unknown	1 (1.8)
Body mass index (kg/m²), mean (SD)	29.5 (6.7)
Oxybate type at study entry, n (%)	
Naive[d]	42 (76.4)
Low-sodium oxybate	6 (10.9)
Sodium oxybate	5 (9.1)
Once-nightly sodium oxybate	2 (3.6)
Concomitant alerting agent , n (%)[e,f,g]	31 (56.4)

[a]Safety analysis set. [b]For additional demographic information, including concomitant alerting agent use, please see **Poster 393**. [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]It is not known whether these agents were 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.
BL, baseline; LXB, low-sodium oxybate; SD, standard deviation.

- A total of 16 (47.1%) participants with NT1 and 18 (52.9%) participants with NT2 were included in the completer analysis set (13 participants in the narcolepsy cohort transferred to a different study cohort)

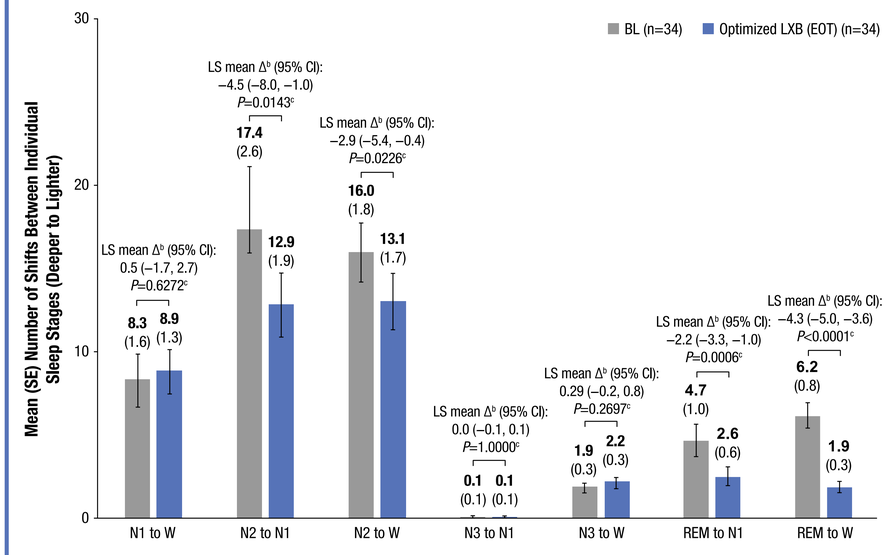
Figure 3. Total Number of Shifts From Deeper to Lighter Sleep Stages Decreased From Baseline to End of Treatment[a,b]



[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. *Controlled for multiplicity.
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.

- **Total shifts index** (total shifts/h of total sleep time):
  - Mean (SE): 6.5 (0.5) at BL and 4.7 (0.4) at EOT; LS mean change (95% CI) from baseline: −1.8 (−2.4, −1.1); *P*<0.0001

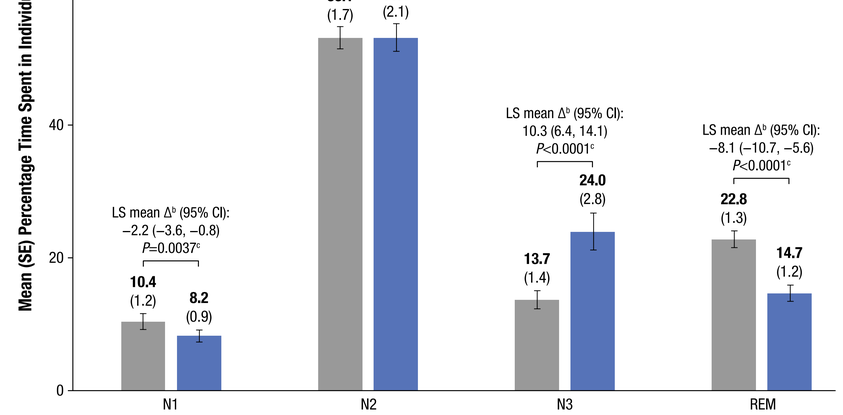
Figure 4. Shifts (Deeper to Lighter) From Individual Sleep Stages Generally Decreased From Baseline to End of Treatment[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal, unless part of the sequential testing strategy.
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, REM to N1, and REM to W were observed

Figure 5. Time (Percentage of TST) Spent in N1 and REM Decreased While Time 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, unless part of the sequential testing strategy.
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.

- The mean (SE) time spent in each sleep stage was:
  - N1: 45.3 (4.9) minutes at BL and 37.2 (4.3) minutes at EOT; LSM change (95% CI): −8.1 (−14.9, −1.4); *P*=0.0196 (nominal)
  - N2: 241.8 (10.5) minutes at BL and 243.3 (13.0) minutes at EOT; LSM change (95% CI): 1.5 (−23.6, 26.6); *P*=0.9040 (nominal)
  - N3: 61.1 (6.0) minutes at BL and 106.1 (11.9) minutes at EOT; LSM change (95% CI): 45.0 (27.0, 63.0); *P*<0.0001 (controlled for multiplicity)
  - REM: 105.0 (7.3) minutes at BL and 65.8 (5.7) minutes at EOT; LSM change (95% CI): −39.2 (−50.8, −27.5); *P*<0.0001 (nominal)

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

Parameter	BL, mean (SE) (n=34)	Optimized LXB (EOT), mean (SE) (n=34)	LS mean Δ[b] (95% CI)	*P* value[c]
Time in bed (min)	531.0 (12.9)	544.6 (11.5)	13.6 (−7.6, 34.9)	0.2010
Total sleep time (min)	453.2 (13.7)	452.4 (12.0)	−0.8 (−23.7, 22.1)	0.9451
Sleep efficiency (%)	85.3 (1.6)	83.2 (1.4)	−2.1 (−4.8, 0.7)	0.1335
Sleep onset latency (min)	14.1 (2.8)	18.9 (3.1)	4.8 (−1.5, 11.2)	0.1320
REM onset latency (min)	103.4 (14.5)	137.4 (18.8)	34.4 (-3.3, 72.1)	0.0722

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

- Total sleep time, sleep efficiency, sleep onset latency, and REM onset latency appeared stable with LXB treatment

Table 3. Treatment-Emergent Adverse Events[a,b]

Participants, n (%)	Total (N=55)
With ≥1 TEAE	34 (61.8)
With ≥1 TEAE related to treatment	30 (54.5)
TEAEs occurring in ≥5% of participants	
Nausea	13 (23.6)
Dizziness	8 (14.5)
Headache	7 (12.7)
Somnolence	6 (10.9)
Vomiting	6 (10.9)
Anxiety	4 (7.3)
Nasal congestion	4 (7.3)
Oropharyngeal pain	4 (7.3)
Brain fog	3 (5.5)
Cough	3 (5.5)
Decreased appetite	3 (5.5)
Enuresis	3 (5.5)
Hypoesthesia	3 (5.5)

[a]Safety analysis set. [b]For additional safety information, please see **Poster 393.**
TEAE, treatment-emergent adverse event.

- No participants had a serious treatment-emergent adverse event

Conclusions

- Participants with narcolepsy taking open-label LXB demonstrated changes in duration and percentage of individual sleep stages, consistent with previous oxybate studies
  - N3 duration/percentage significantly increased with LXB; this increase may contribute to daytime symptom improvements both through addressing known N3 deficiencies and through the restoration of slow wave sleep dynamics that improve sleep consolidation[10,11]
  - REM duration/percentage significantly decreased with LXB, consistent with previous oxybate studies[12,13]
  - Changes in mean total sleep time and N2 duration/percentage were negligible
- Participants with narcolepsy taking open-label LXB had fewer shifts from deeper to lighter stages of sleep, suggesting improvement in DNS
- Limitations of the DUET study include: 1) the open-label, single-arm design, which limits 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 the impact of LXB treatment on sleep architecture in individuals with narcolepsy and are consistent with the known effects of oxybates on sleep architecture[3]

References: 1. Roth T, et al. *J Clin Sleep Med.* 2013;9(9):955-965. **2.** Maski K, et al. *J Clin Sleep Med.* 2022;18(1):289-304. **3.** Roth T, et al. *Sleep Med.* 2024;114:255-265. **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. 2012. 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. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **8.** 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. **9.** Carskadon MA, Dement WC. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine.* 5th ed. St. Louis, MO: Elsevier Saunders; 2011:16-26. **10.** Khatami R, et al. *Sleep.* 2007;30(8):980-989. **11.** Khatami R, et al. *Sleep.* 2008;31(6):859-867. **12.** Black J, et al. *Sleep Med.* 2009;10:829-835. **13.** Roth T, et al. *CNS Drugs.* 2022;36:377-387.

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Supplemental Statistical Methods

- Formal hypothesis testing was conducted using the completer analysis set for the following endpoints:
  1. Epworth Sleepiness Scale (ESS) score (decrease from baseline [BL])
  2. Total sleep stage shifts from N1/N2/N3/rapid eye movement [REM] to wake and N2/N3/REM to N1 (decrease from BL)
  3. Duration of N3 sleep (increase from BL)
  4. Total number of nocturnal awakenings (decrease from BL)
- Decreases or increases from BL 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 (EOT) visit, was compared against a null hypothesis value of 0.
- Multiplicity control was achieved using a sequential testing strategy conducted separately for each cohort. Listed endpoints were tested in the order shown above. 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 8–13 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 4–7 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 stage N3 sleep
- **Stage N3:** an EEG (epoch) with ≥20% of an epoch consisting of slow, high amplitude waveforms of 0.5–2 Hz and peak-to-peak amplitude of >75mV.
- **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:** 2 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 idiopathic hypersomnia cohort presented in **Poster 415**
- PSG Arousals from the narcolepsy cohort presented in **Poster 556**
- Effectiveness and safety of LXB dosages >9 g/night in narcolepsy in **Poster 558**