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

DUET STUDY 407

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Introduction

- Disrupted nighttime sleep, one of the pentad of classical symptoms of narcolepsy,[1,2] includes polysomnography [PSG]-based evidence of frequent stage shifts from deeper to lighter sleep stages, wake to rapid eye movement (REM) sleep transitions, increased stage 1 sleep, and frequent awakenings and arousals, as well as patient-reported poor sleep quality.[2,3] Sleep can also be disturbed by sleep paralysis and sleep-related hallucinations (hypnagogic and hypnopompic)[2,4]
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration to treat excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy and idiopathic hypersomnia in adults[5-8]
- 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 treatment on daytime and nighttime outcomes, including sleep quality (using PSG and self-reported diaries) in participants with narcolepsy or idiopathic hypersomnia

Objective

- This analysis evaluated the effectiveness of LXB on self-reported sleep quality and morning sleepiness/alertness in participants with narcolepsy in the DUET study

Methods

- DUET included adult participants (18–75 years of age, inclusive) with a primary diagnosis of narcolepsy (type 1 or 2) per *International Classification of Sleep Disorders – Third Edition* (ICSD-3)[9] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[4] criteria

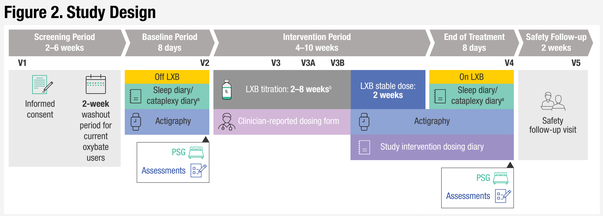
Figure 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion 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	• 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 participant's safety or interfere with study conduct

[a]At screening visit 1 or an ESS score >10 after the washout period, if taking an oxybate medication. [b]Hypopnea definition included a ≥4% desaturation per *The AASM Manual for the Scoring of Sleep and Associated Events*,[10] as assessed during BL PSG visit.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; BL, baseline; 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.

- DUET included a screening period (2-week washout for current oxybate users), an 8-day BL period (ending with an overnight BL PSG visit with additional assessments), a 2- to 8-week LXB titration period, a 2-week stable-dose period (SDP), an 8-day end-of-treatment (EOT) assessment period while participants were taking their optimized stable dose of LXB (ending with an overnight EOT PSG with additional assessments), and a 2-week safety follow-up
  - All participants with narcolepsy took LXB twice nightly (per the US prescribing label)[5]
- Participants underwent nocturnal PSG (*ad libitum* protocol) at BL and EOT
- The morning after the PSG, the Karolinska Sleepiness Scale (KSS; an exploratory outcome) was administered 90 minutes post-awakening (with other assessments)
  - The KSS measures situational sleepiness in the last 10 minutes using a 9-point scale (1="extremely alert" to 9="very sleepy, great effort to keep awake, fighting sleep")[11]
- Participants completed a daily electronic sleep diary (eDiary) during the BL and EOT periods, including questions regarding nightly sleep patterns, nocturnal total sleep time, and sleep quality (5-point scale; "very good" to "very poor"; exploratory outcomes), as well as how rested/refreshed they felt upon awakening (5-point scale; "very well" to "not at all"; secondary outcome)
  - Completion of ≥5 eDiary days during the 8-day assessment before PSG visits was required for analysis

Figure 2. Study Design



[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). Investigator could optimize participant dosage and move participant to stable dose at visit 3, 3A, or 3B but not during intervening weekly teleconferences.
LXB, low-sodium oxybate; PSG, polysomnography; V, visit.

- *P* values reported are nominal and are not adjusted for multiplicity
- Safety endpoints included incidence and severity of treatment-emergent adverse events (TEAEs)
- 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

Results

Table 1. Demographics and Baseline Characteristics for Enrolled Participants With Narcolepsy[a]

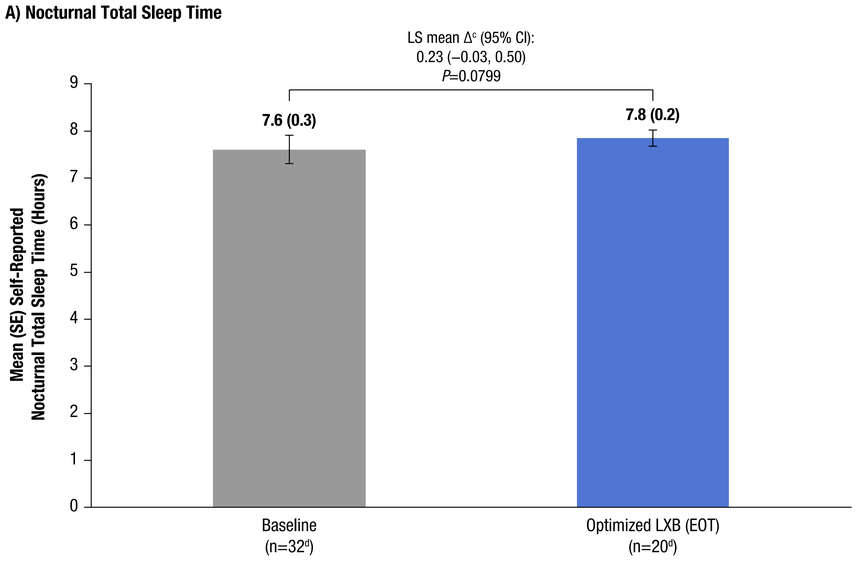
Characteristic	NT1 (n=26)	NT2 (n=29)	Total Narcolepsy Cohort (N=55)
Age (years), mean (SD)	34.6 (12.6)	32.4 (13.2)	33.4 (12.9)
Sex at birth, n (%)			
Male	7 (26.9)	8 (27.6)	15 (27.3)
Female	19 (73.1)	21 (72.4)	40 (72.7)
Race, n (%)			
White	19 (73.1)	25 (86.2)	44 (80.0)
Black or African American	4 (15.4)	3 (10.3)	7 (12.7)
American Indian or Alaska Native	0	0	0
Asian	2 (7.7)	0	2 (3.6)
Native Hawaiian or other Pacific Islander	0	0	0
Multiple[b]	0	1 (3.4)	1 (1.8)
Unknown	1 (3.8)	0	1 (1.8)
Body mass index (kg/m²), mean (SD)	30.3 (6.9)	28.7 (6.6)	29.5 (6.7)
Oxybate type at study entry, n (%)			
Naive[c]	18 (69.2)	24 (82.8)	42 (76.4)
Low-sodium oxybate	3 (11.5)	3 (10.3)	6 (10.9)
Sodium oxybate	3 (11.5)	2 (6.9)	5 (9.1)
Once-nightly sodium oxybate	2 (7.7)	0	2 (3.6)
Oxybate total nightly dosage at screening[d] (g)			
Mean (SD)	7.1 (1.4)	8.0 (1.2)	7.4 (1.4)
Median (min, max)	6.5 (5.6, 9.0)	8.0 (7.0, 9.0)	7.0 (5.6, 9.0)

[a]Safety analysis set. [b]One participant reported >1 race. [c]No oxybate use within 2 weeks of entering the study. [d]For the 13 participants who were taking an oxybate at screening and prior to washout.
max, maximum; min, minimum; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

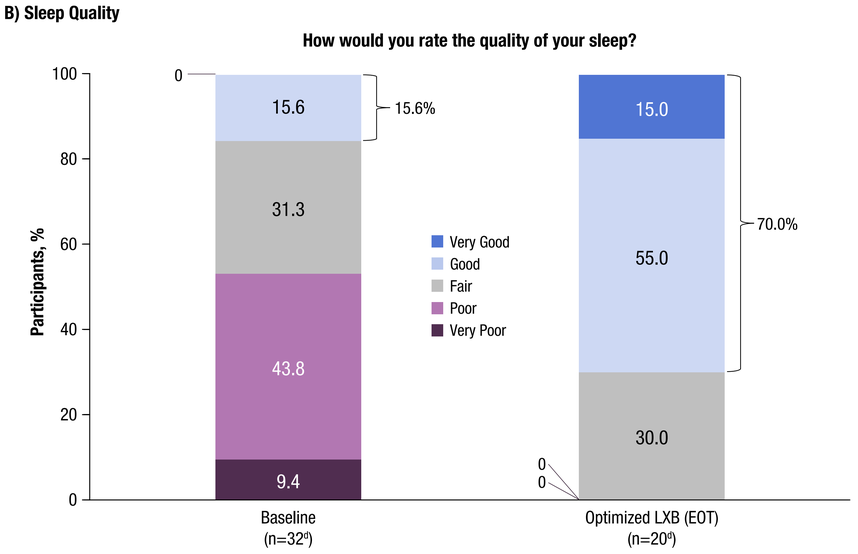
- The completer analysis set included 34 participants with narcolepsy (NT1, n=16 [47.1%]; NT2, n=18 [52.9%])
- Thirteen participants in the narcolepsy cohort transferred to a different study cohort (reported elsewhere), and 8 participants discontinued the study

Figure 3. eDiary[a] Self-Reported Nocturnal Total Sleep Time (A), Sleep Quality (B), and Level of Rested Sleep (C)[b]

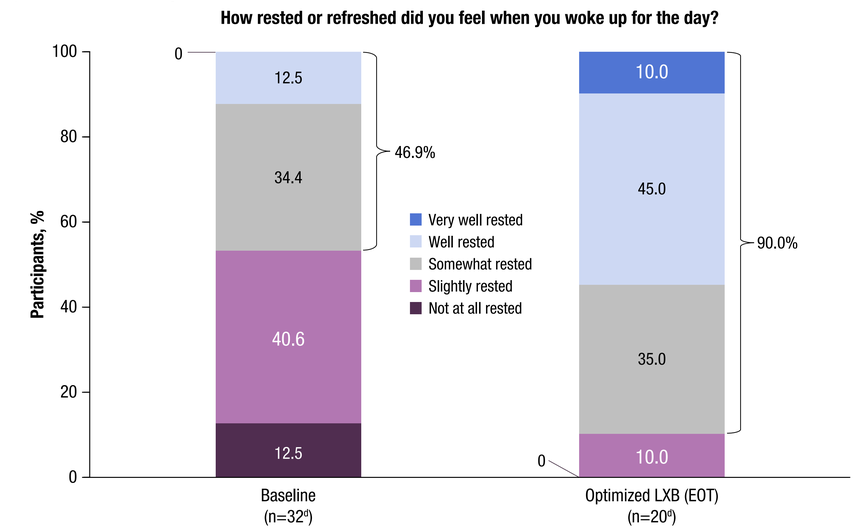
A) Nocturnal Total Sleep Time



B) Sleep Quality



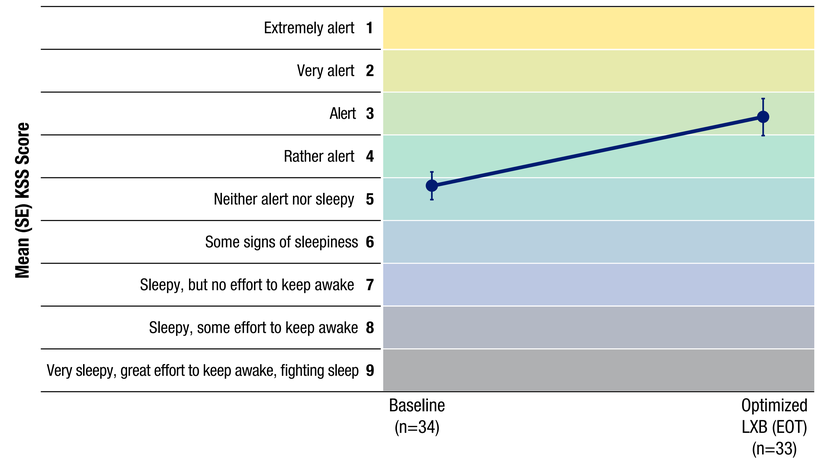
C) Level of Rested Sleep



[a]In the 8 days prior to and including the BL and EOT PSGs. [b]Completer analysis set. [c]Difference between BL and EOT, based on 20 participants who completed the assessment at both BL and EOT. [d]Not all participants completed all daily eDiary assessments.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; PSG, polysomnography; SE, standard error.

- Mean (standard error [SE]) eDiary self-reported nocturnal total sleep time in the 8 days prior to and including the BL and EOT PSGs was 7.6 (0.3) hours at BL and 7.8 (0.2) hours at EOT
  - Some eDiary assessments were missing due to technical issues, resulting in eDiary data not meeting the minimum threshold for analysis
- The percentage of participants rating their sleep quality as "very good"/"good" was 15.6% at BL and 70.0% at EOT
  - No participants reported poor or very poor sleep quality at EOT
- The percentage of participants with rested sleep ("very well"/"well"/"somewhat" rested) was 46.9% at BL and 90.0% at EOT

Figure 4. Sleepiness/Alertness Ratings on the Karolinska Sleepiness Scale at 90 Minutes Post-Awakening[a]



[a]Completer analysis set.
EOT, end of treatment; KSS, Karolinska Sleepiness Scale; LXB, low-sodium oxybate; SE, standard error.

- Mean (SE) sleepiness rating on the KSS at 90 minutes post-awakening from the overnight PSG was 5.1 (0.3) at BL and 3.6 (0.4) at EOT

Table 2. Mean Nightly LXB Dosage During Stable-Dose Period[a]

Mean (SD), grams	NT1 (n=16)	NT2 (n=20)	Total Narcolepsy Cohort (N=36[b])
Twice-nightly dosage	7.3 (1.2)	6.9 (1.9)	7.0 (1.6)
First nightly LXB dosage	3.8 (0.7)	3.6 (1.0)	3.7 (0.9)
Second nightly LXB dosage	3.5 (0.6)	3.3 (1.1)	3.4 (0.9)

[a]Includes all participants from the safety analysis set who reached the SDP.
LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; SDP, stable-dose period.

- Once a participant reached an optimized dosage, they continued this dosage as a stable regimen during the SDP and EOT period
- 7.0 g/night was the average optimized twice-nightly total dosage

Table 3. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Total (N=55)
With ≥1 TEAE	34 (61.8)
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.
TEAE, treatment-emergent adverse event.

- Thirty-four (61.8%) participants with narcolepsy reported a TEAE
  - TEAEs were mild or moderate in severity
  - There were no serious adverse events

Conclusions

- Following open-label LXB treatment, participants with narcolepsy reported improved sleep quality and, upon awakening, feeling more rested. At EOT, compared with BL, approximately 4.5 times as many study participants rated their sleep quality as "good"/"very good," and nearly twice as many study participants rated themselves as "somewhat"/"well"/"very well" rested or refreshed upon awakening
- The KSS and self-reported eDiary assessments provide a subjective participant perspective on the changes occurring with LXB treatment
- Limitations of the DUET study include 1) the open-label design and lack of a control cohort, which limit ability to solely attribute findings 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
- TEAEs were consistent with the known safety profile of LXB

References: 1. Maski KP, et al. *Sleep.* 2021;44(7):zsab021. **2.** Maski K, et al. *J Clin Sleep Med.* 2022;18(1):289-304. **3.** Pizza F, et al. *Sleep.* 2015;38(8):1277-1284. **4.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013. **5.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **6.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **7.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **8.** 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-phosphorushuman-over-counter-and-prescription-drug. **9.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **10.** 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. **11.** Shahid A, et al. *STOP, THAT and One Hundred Other Sleep Scales.* New York, NY: Springer New York; 2012:209-210.

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