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

DUET STUDY 407

Richard K. Bogan, MD, FCCP, FAASM[1]; David T. Plante, MD, PhD[2]; Alyssa Cairns, PhD[3]; Deborah A. Nichols, MS[4]; Teresa L. Steininger, PhD[4]; Douglas S. Fuller, MS[3]; Sarah Akerman, MD[3]; Marisa Whalen, PharmD[3]; Nancy Foldvary-Schaefer, DO, MS[5]

[1]University of South Carolina School of Medicine, Columbia, SC, USA; [2]University of Wisconsin-Madison, Madison, WI, USA; [3]Jazz Pharmaceuticals, Philadelphia, PA, USA; [4]Jazz Pharmaceuticals, Palo Alto, CA, USA; [5]Sleep Disorders Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Introduction

- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration to treat idiopathic hypersomnia in adults and excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy[1-4]
- Idiopathic hypersomnia is associated with excessive daytime sleepiness, and many patients report that their sleep is nonrestorative.[5,6] Additionally, sleep inertia (including prolonged difficulty awakening and repeated returns to sleep) is reported; in some individuals with idiopathic hypersomnia, self-reported total (24-hour) sleep time may exceed 10 hours[6-9]
- 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 polysomnography [PSG] and self-reported diaries), in participants with idiopathic hypersomnia or narcolepsy

Objective

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

Methods

- DUET included adult participants (18–75 years of age, inclusive) with a primary diagnosis of idiopathic hypersomnia

Figure 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- 18–75 years of age with primary diagnosis of idiopathic hypersomnia per *International Classification of Sleep Disorders – Third Edition* criteria[a]
  - Individuals with and without long sleep time were included[a]
- ESS score >10[a]
- 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

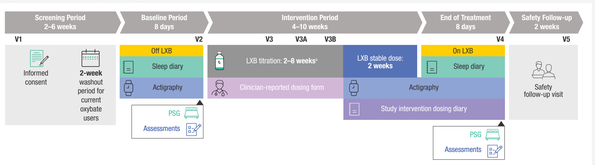
Key Exclusion Criteria

- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[a]
- History/presence of other untreated/inadequately treated or unstable/clinically significant condition that might affect participant safety or interfere with study conduct (eg, a sleep, behavioral, psychiatric, or neurologic disorder)

[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 a ≥4% desaturation per *The AASM Manual for the Scoring of Sleep and Associated Events*;[10] as assessed during baseline PSG visit.
AHI, apnea-hypopnea index; AASM, American Academy of Sleep Medicine; ESS, Epworth Sleepiness Scale; PSG, polysomnography.

- DUET comprised a screening period (2-week washout for current oxybate users), an 8-day baseline (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
  - Study investigators had the option of treating with a once- or twice-nightly LXB regimen in the idiopathic hypersomnia cohort (per the US prescribing label)[1]
- 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 an electronic sleep diary (eDiary) daily during the BL and EOT periods, including questions regarding nightly sleep patterns, nocturnal total sleep time, sleep quality (5-point scale; "very good" to "very poor"; exploratory outcomes), and how rested/refreshed the participant 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]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 SDP 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 Idiopathic Hypersomnia[a]

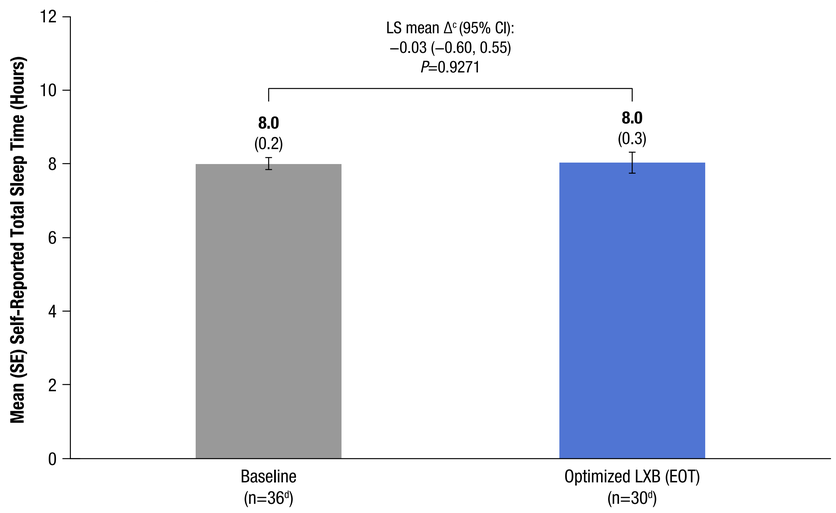
Characteristic	Total (N=46)
Age (years), mean (SD)	38.1 (11.8)
Sex at birth, n (%)	
Male	9 (19.6)
Female	37 (80.4)
Race, n (%)	
White	39 (84.8)
Black or African American	3 (6.5)
American Indian or Alaska Native	0
Asian	2 (4.3)
Native Hawaiian or other Pacific Islander	1 (2.2)
Multiple[b]	1 (2.2)
Body mass index (kg/m²), mean (SD)	28.5 (6.4)
Oxybate type at study entry, n (%)	
Naive[c]	37 (80.4)
Low-sodium oxybate	9 (19.6)
Sodium oxybate	0
Once-nightly sodium oxybate	0
Oxybate total nightly dosage at screening[d] (g)	
Mean (SD)	6.8 (2.2)
Median (min, max)	6.8 (3.8, 9.0)

[a]Safety analysis set. [b]Participant reported >1 race. [c]No oxybate use within 2 weeks of entering the study. [d]For the 9 participants who were taking an oxybate at screening and prior to washout.
BL, baseline; max, maximum; min, minimum; SD, standard deviation.

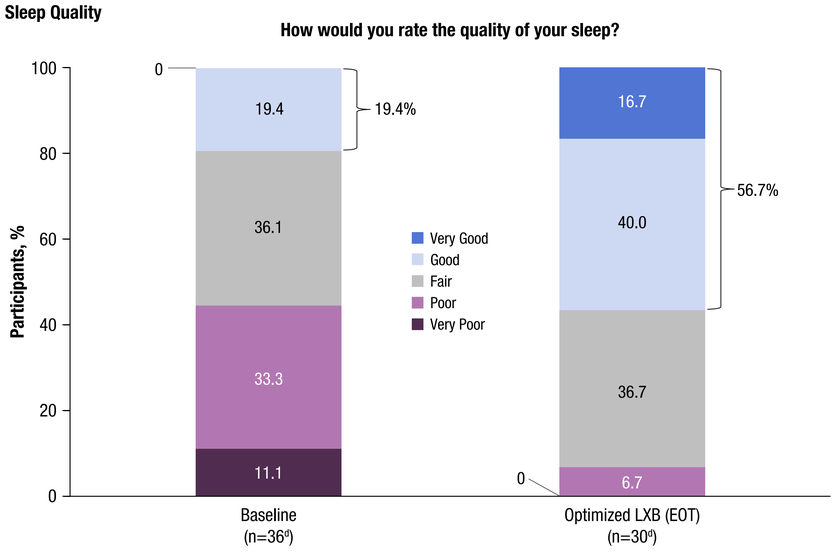
- Forty-six participants with idiopathic hypersomnia enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period; most were female (80.4%) and White (84.8%)

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

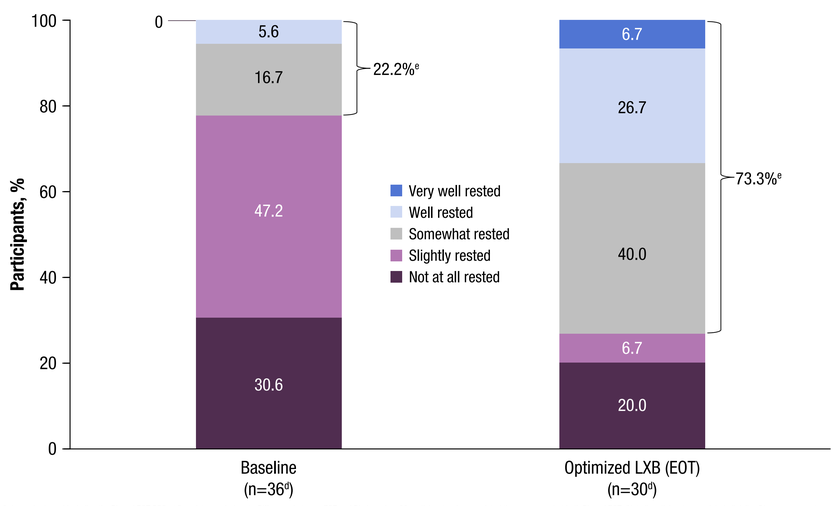
A) Nocturnal Total Sleep Time



B) Sleep Quality



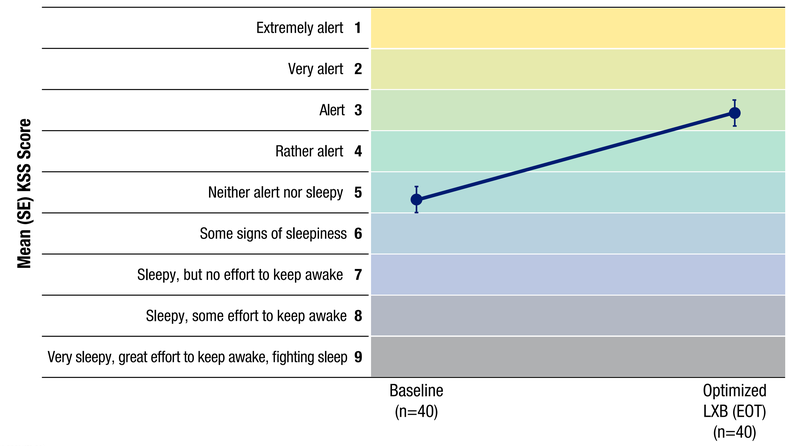
C) Level of Rested Sleep



[a]In the 8 days prior to and including the BL and EOT PSGs. [b]Completer analysis set. [c]Difference between EOT and BL, based on 30 participants who completed the assessment at both BL and EOT. [d]Not all participants completed all daily eDiary assessments. [e]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; PSG, polysomnography; SE, standard error.

- eDiary self-reported nocturnal total sleep time in the 8 days prior to and including the BL and EOT PSGs remained stable from BL to EOT: mean (SE) 8.0 (0.2) and 8.0 (0.3) hours, respectively
  - 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 19.4% at BL and 56.7% at EOT
- The percentage of participants with rested sleep ("very well"/"well"/"somewhat" rested) was 22.2% at BL and 73.3% at EOT

Figure 4. Sleepiness/Alertness Ratings on the Karolinska Sleepiness Scale 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 5.7 (0.3) at BL and 3.6 (0.3) at EOT

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

Mean (SD), grams	Idiopathic Hypersomnia Cohort (N=41[a])
Once-nightly LXB (n=15)	
Mean (SD)	4.8 (1.1)
Twice-nightly LXB (n=26)	
Mean (SD)	7.7 (1.2)
First nightly LXB dose	4.0 (0.8)
Second nightly LXB dose	3.6 (0.8)

[a]Includes participants from the safety analysis set who reached the SDP.
LXB, low-sodium oxybate; 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
- Fifteen participants (36.6%) were taking LXB once nightly and 26 participants (63.4%) were taking LXB twice nightly

Table 3. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Total (N=46)
With ≥1 TEAE	34 (73.9)
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.
TEAE, treatment-emergent adverse event.

- Thirty-four participants (73.9%) with idiopathic hypersomnia reported a TEAE
  - TEAEs were mild or moderate in severity
  - There was 1 serious AE in the idiopathic hypersomnia cohort (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

- Following open-label LXB treatment, participants with idiopathic hypersomnia reported improved sleep quality and, upon awakening, feeling more rested. At EOT, compared with BL, approximately 3 times as many study participants rated their sleep quality as "good"/"very good" and themselves as "somewhat"/"well"/"very well" rested or refreshed upon awakening. These data also support a benefit of open-label LXB on sleep inertia
- 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 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
- TEAEs were consistent with the known safety profile of LXB

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **3.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **4.** 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. **5.** Roth B, et al. *Arch Gen Psychiatry.* 1972;26(5):456-462. **6.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **7.** Trotti LM. *Sleep Med Clin.* 2017;12(3):331-344. **8.** Vernet C, Arnulf I. *Sleep.* 2009;32(6):753-759. **9.** Vernet C, et al. *J Sleep Res.* 2010;19(4):525-534. **10.** American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* 2.5 ed. Darien, IL: American Academy of Sleep Medicine; 2018. **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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