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DUET STUDY 407

Patient-Reported Improvement in Hypersomnolence Measures in Participants With Narcolepsy Taking >9 Gram Dosage of Low-Sodium Oxybate in the DUET Study

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Objective

- To evaluate changes in patient-reported hypersomnolence measures in participants with narcolepsy taking low-sodium oxybate (LXB) >9 g/night compared with an LXB 9 g/night baseline

Conclusions

- Participants with narcolepsy who, in the opinion of the investigator, could benefit from continued titration >9 g and were optimized to LXB >9 g/night, reported improved sleep quality and restfulness that paralleled improvements in daytime sleepiness and functioning, relative to 9 g/night
- Treatment-emergent adverse events with higher LXB dosages (>9–12 g/night) were consistent with those at lower dosages (≤9 g/night)
- Limitations include that effectiveness analyses were not powered for formal comparisons and were based on the completer analysis set, which may not represent the experience of all individuals who take dosages >9 g/night
- DUET fills an important knowledge gap by assessing LXB dosages >9 g/night and changes in patient perception of a wide range of symptoms, providing insight into the benefit and safety of dosages up to 12 g/night and supporting individualized clinical decision-making

References: 1. Weaver TE, et al. *J Sleep Res.* 2021;30(3):e13210. **2.** Flores NM, et al. *J Clin Sleep Med.* 2016;12(3):401-407. **3.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **4.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2025. **5.** Ohayon MM, et al. Presented at: Annual Scientific Meeting of the Associated Professional Sleep Societies; June 8-12, 2019; San Antonio, TX. **6.** Schneider LD, et al. *Neurol Ther.* 2026; In Press. **7.** Plante DT, et al. *CNS Drugs.* 2026; Mar 14 Online Ahead of Print. **8.** Troester MM, 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.** Johns MW. *Sleep.* 1991;14(6):540-545. **10.** Maski K, et al. *J Clin Sleep Med.* 2021;17(9):1895-1945. **11.** Chasens ER, et al. *Sleep.* 2009;32(7):915-919.

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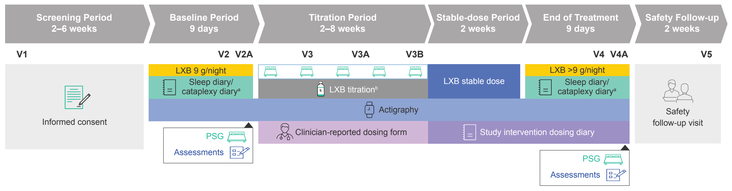
Introduction

- Narcolepsy is a central disorder of hypersomnolence characterized by a wide range of symptoms, including excessive daytime sleepiness (EDS), cataplexy, disrupted nighttime sleep (DNS), hypnagogic and hypnopompic hallucinations, and sleep paralysis, that can impair daytime functioning[1-3]
- LXB (Xywav®) is approved by the US Food and Drug Administration to treat EDS or cataplexy in patients ≥7 years of age with narcolepsy and for the treatment of idiopathic hypersomnia in adults[4]
  - The recommended dosage range is 6 g to 9 g/night, gradually titrated based on efficacy and tolerability[4]
  - Dosages higher than 9 g/night are not included in the prescribing information and have not been studied extensively; however, a retrospective analysis of adults enrolled in the Risk Evaluation and Mitigation Strategy (REMS) database for LXB found that 1% of patients were taking total nightly dosages >9 g/night (see **Poster 529** during Session P-41), and real-world data from the Nexus Registry reported that 4.1% of patients taking sodium oxybate were taking a dosage of >9 g/night[5]
- DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, single-arm, open-label study (NCT05875974) of LXB treatment in participants with narcolepsy (type 1 [NT1] or type 2 [NT2]) or idiopathic hypersomnia
  - Results for the narcolepsy and idiopathic hypersomnia cohorts have been reported previously[6,7]
  - DUET included a >9 g cohort; participants with narcolepsy currently taking 9 g of LXB who, in the opinion of the investigator, would likely benefit from continued titration, could enter the >9 g cohort and titrate from 9 g to an optimized dosage up to 12 g (twice nightly; maximum of 4.5 g for the second dose)

Methods

Figure 1. Study Design



[a]Cataplexy diary in narcolepsy type 1 only. [b]Weekly titration visits with a dose escalation were performed as an overnight PSG visit for safety monitoring; visits without a dose escalation could be via teleconference. Titration could take between 2 and 8 weeks. Visit 3 occurred on titration day 14. 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 the stable-dose period at visit 3, 3A, or 3B, but not during intervening weekly teleconferences.
LXB, low-sodium oxybate; PSG, polysomnography; V, visit.

- Participants taking LXB 9 g at screening and who, in the opinion of the investigator, may benefit from continued titration could enter the >9 g narcolepsy cohort 1 of 2 ways: *direct enrollment* (participants who were taking LXB 9 g/night at screening) or *transfer* (participants who already enrolled in the narcolepsy cohort and had titrated up to 9 g/night)
- The 9-day baseline (BL) period on LXB 9 g/night ("LXB 9 g BL") and 9-day end-of-treatment (EOT) period on an optimized stable dose of LXB ("optimized LXB >9 g EOT") included 8 days of daily assessments ending with overnight polysomnography (PSG) with additional assessments

LXB Titration Requirements

Investigators titrated LXB to an optimal dosage for participants in the >9g cohort under the following requirements:
- The first night for all LXB dose escalations above 9 g was conducted in the sleep laboratory clinic with PSG and appropriate in-clinic safety monitoring
- Each dose-escalation step during titration was limited to increases of 0.5 g/night/week, up to a maximum of 12 g nightly
- All participants took twice-nightly LXB
  - The first nightly maximal dose was 7.5 g
  - The second nightly maximal dose was 4.5 g and was administered approximately 4 hours after the first dose

LXB, low-sodium oxybate; PSG, polysomnography.

- During titration (dosage escalation), mean (SD) number of safety PSGs conducted for each participant was 4.5 (1.7) (median, 5.0; min, 1; max, 6)

Results

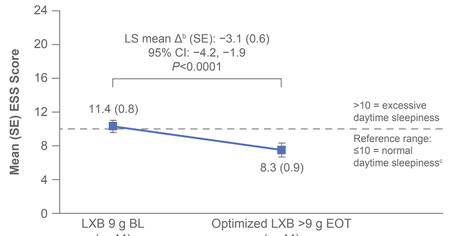
Table 1. Demographics and Baseline Characteristics[a]

Characteristic	Total >9 g Cohort (N=48)
Age, years	
Mean (SD)	39.2 (10.9)
Median (min, max)	38.0 (18, 65)
Sex at birth, n (%)	
Male	30 (62.5)
Female	18 (37.5)
Race, n (%)	
White	37 (77.1)
Black or African American	7 (14.6)
Asian	1 (2.1)
Multiple[b]	2 (4.2)
Unknown	1 (2.1)
Ethnicity, n (%)	
Hispanic or Latino	1 (2.1)
Not Hispanic or Latino	47 (97.9)
Body mass index (kg/m^2), mean (SD)	29.9 (8.9)
Comorbid OSA,[c] n (%)	15 (31.3)
Concomitant alerting agent use,[d] n (%)	28 (58.3)

[a]Safety analysis set (all participants who enrolled in the study and took their prescribed LXB regimen for ≥1 night after the LXB 9 g BL period [N=48]). [b]Participant reported >1 race. [c]Based on medical history and treatment records at screening and/or technical notes from any PSG visit in which positive airway pressure treatment settings or oral appliances may have been mentioned. [d]Participants could have been taking multiple different alerting medications. It is not known whether these agents were prescribed for excessive sleepiness, narcolepsy, or another condition. Concomitant medications were started prior to the first dose of LXB and were ongoing throughout the study.
BL, baseline; max, maximum; min, minimum; LXB, low-sodium oxybate; OSA, obstructive sleep apnea; PSG, polysomnography; SD, standard deviation.

- Mean (SD) nightly LXB dosage during the stable-dose period (n=45) was 11.1 (1.0) g/night
- 46.7% (n=21/45) of participants reached a stable total LXB dosage of 12 g/night

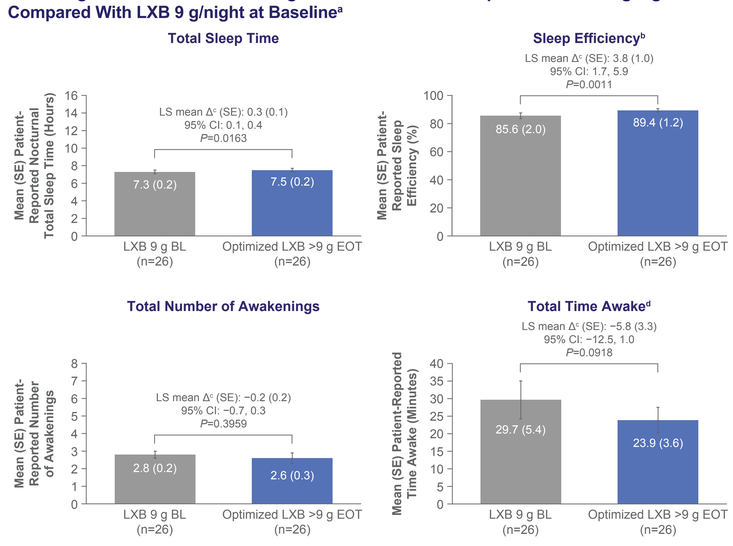
Figure 2. Participants Reported Improved Excessive Daytime Sleepiness With Optimized LXB >9 g/night Compared With LXB 9 g/night at Baseline[a]



[a]Completer analysis set (all participants who enrolled in the study, took their prescribed LXB regimen for ≥1 night after the LXB 9 g BL period, completed the stable-dose period, and completed the optimized LXB >9 g EOT PSG visit [n=44]). [b]Difference between LXB 9 g BL and optimized LXB >9 g EOT. LS mean differences and 95% CI were calculated using a mixed model with repeated measures of change from LXB 9 g BL to optimized LXB >9 g EOT, adjusted for the LXB 9 g BL value. No formal hypothesis testing was planned for the >9 g cohort; therefore, *P* values are nominal. [c]Established categories consider scores up to 10 normal.[9]
AASM, American Academy of Sleep Medicine; BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; MCID, minimal clinically important difference; PSG, polysomnography; SE, standard error.

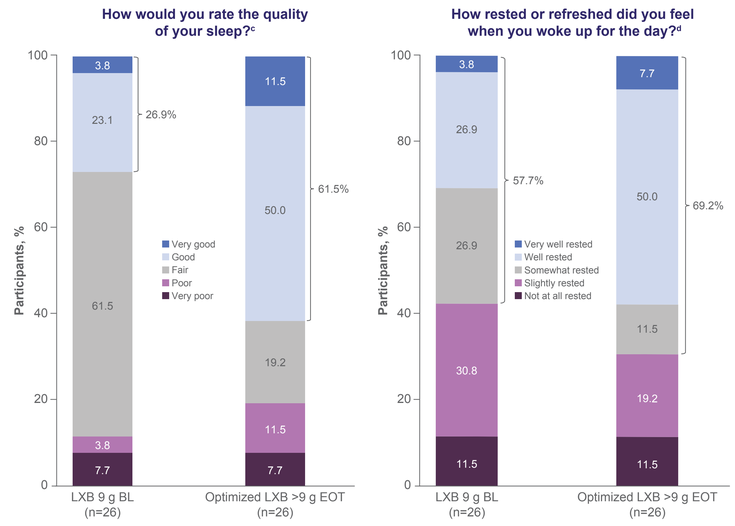
- ESS scores improved by 3 points, which exceeds the AASM clinical significance threshold (2 points),[10] and mean population scores improved to within the reference range for normal daytime sleepiness levels (≤10)

Figure 3. Participants Reported Longer Total Sleep Time, Better Sleep Efficiency, and No Change in Number of Awakenings or Time Awake With Optimized LXB >9 g/night Compared With LXB 9 g/night at Baseline[a]



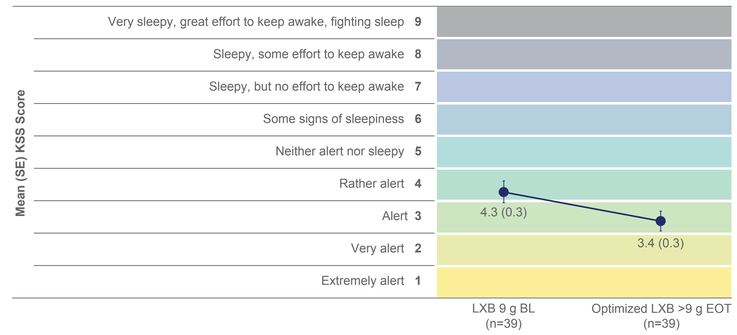
[a]Assessed with sleep eDiary (completed during the 8-day assessment prior to the BL and EOT visits) in completer analysis set; to be included in this analysis, participants needed at least 5 days of eDiary data. [b]TST divided by time in bed. [c]Difference between LXB 9 g BL and optimized LXB >9 g EOT. LS mean differences and 95% CI were calculated using a mixed model with repeated measures of change from LXB 9 g BL to optimized LXB >9 g EOT, adjusted for the LXB 9 g BL value. No formal hypothesis testing was planned for the >9 g cohort; therefore, *P* values are nominal. [d]Based on the response to the question, "Adding up all awakenings last night, in total, how many minutes were you awake?"
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; SE, standard error; TST, total sleep time.

Figure 4. A Greater Percentage of Participants Rated Their Sleep Quality as Good or Very Good and Reported Feeling Well or Very Well Rested With Optimized LXB >9 g/night Compared With LXB 9 g/night at Baseline[a,b]



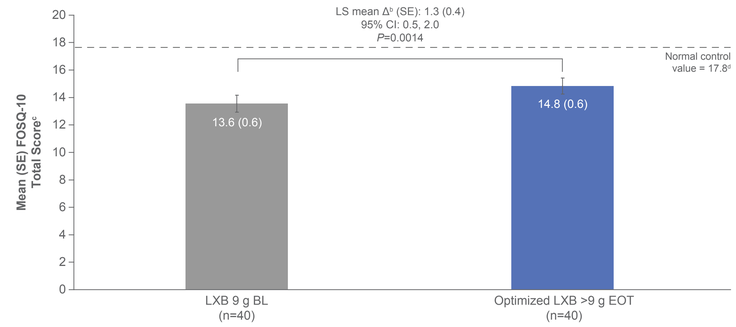
[a]Assessed with sleep eDiary in completer analysis set. [b]In the 8 days prior to and including the LXB 9 g and optimized LXB >9 g PSGs. [c]Rated on a 5-point scale of "very good" to "very poor." [d]Rated on a 5-point scale of "very well rested" to "not at all rested."
BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate; PSG, polysomnography.

Figure 5. Participants Reported Greater Situational Alertness at 90-min Post Awakening With Optimized LXB >9 g/night Compared With LXB 9 g/night at Baseline[a,b]



[a]Assessed with the KSS in completer analysis set. [b]Administered 90 minutes post-PSG awakening.
BL, baseline; EOT, end of treatment; KSS, Karolinska Sleepiness Scale; LXB, low-sodium oxybate; min, minutes; PSG, polysomnography; SE, standard error.

Figure 6. Participants Reported Improved Functional Status With Optimized LXB >9 g/night Compared With LXB 9 g/night at Baseline[a]



[a]As assessed with the FOSQ-10 in completer analysis set. [b]Difference between LXB 9 g BL and optimized LXB >9 g EOT. LS mean differences and 95% CI were calculated using a mixed model with repeated measures of change from LXB 9 g BL to optimized LXB >9 g EOT, adjusted for the LXB 9 g BL value. [c]FOSQ-10 total score range is 5–20 points, with higher scores indicating better functional status. [d]The mean (SD) published normative value in individuals who do not experience sleepiness-related impairment is 17.8 (3.1).[11]
BL, baseline; CI, confidence interval; EOT, end of treatment; FOSQ, Functional Outcomes of Sleep Questionnaire; LS, least squares; LXB, low-sodium oxybate; SE, standard error.

- FOSQ-10 scores improved by 1.3 points, which exceeds the AASM clinical significance threshold (1 point)[10]

Treatment-Emergent Adverse Events

- Of 48 participants, 36 (75.0%) experienced ≥1 treatment-emergent adverse event, which were mostly mild or moderate in severity; additional adverse event information can be found in the supplement accessible via the QR code
- One serious treatment-emergent adverse event of severe syncope occurred during a morning blood draw for clinical labs after PSG; it was determined to be unrelated to LXB
- No changes in PSG-measured respiratory assessments (LSM change [95% CI] from LXB 9 g/night BL to optimized LXB >9 g/night EOT) were observed:
  - Apnea-hypopnea index (events/hour): −0.2 (−0.7, 0.4)
  - Central apnea index (events/hour): 0.00 (−0.01, 0.01)
  - Mean SpO_2 (%): 0.0 (−0.2, 0.2)
  - Percentage of total sleep time with SpO_2 <90% (%): −0.3 (−0.4, −0.1)

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Supplemental Results

Supplemental Figure S1. Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults aged 18–75 with a primary diagnosis of NT1 or NT2 (ICSD-3 or DSM-5)
- Taking LXB 9 g at screening and who, in the opinion of the investigator, may benefit from continued titration >9 g
- 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

Exclusion Criteria

- Untreated or inadequately treated sleep-disordered breathing (AHI >10)[a]
  - Participants adequately treated for OSA (AHI ≤10) were eligible and asked to maintain any treatment regimen (eg, positive airway pressure, oral appliance) for the entirety of the study
- History/presence of other untreated, inadequately treated, or unstable disorder or condition (eg, sleep, medical, behavioral/psychiatric, neurologic)[b]
- Medication(s) contraindicated, with known drug-drug interaction, or similar EEG effects as LXB or known to have clinically significant CNS sedating effects

[a]Defined as AHI >10, with hypopnea definition including a ≥4% desaturation as per Rule 1B in *The AASM Manual for the Scoring of Sleep and Associated Events*.[8] [b]As determined by the investigator.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; CNS, central nervous system; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; EEG, electroencephalogram; ICSD-3, *International Classification of Sleep Disorders–Third Edition*; LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OSA, obstructive sleep apnea; PSG, polysomnography.

Supplemental Table S1. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Total >9 g Cohort (N=48)
With ≥1 TEAE	36 (75.0)
With ≥1 treatment-related TEAE	26 (54.2)
TEAEs occurring in ≥5% of participants	
Nausea	6 (12.5)
Vomiting	6 (12.5)
Headache	5 (10.4)
Enuresis	4 (8.3)
Hyperhidrosis	4 (8.3)
Somnolence	4 (8.3)
Diarrhea	3 (6.3)
Fall	3 (6.3)
Hypotension[b]	3 (6.3)
Pollakiuria	3 (6.3)
Upper respiratory tract infection	3 (6.3)

Lowest — Highest

[a]Safety analysis set. [b]The 3 hypotension TEAEs occurred during the overnight LXB 9 g BL PK visit while participants were taking LXB 9 g/night. These events were captured as TEAEs because they occurred on the same date as the first >9 g/night dosage of study intervention (ie, from the night before, after midnight); all 3 TEAEs were moderate in severity, related to study intervention, and resolved. No associated changes in pulse, respiratory rate, or oxygen saturation were recorded in these participants.
BL, baseline; LXB, low-sodium oxybate; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

- One serious treatment-emergent adverse event of severe syncope occurred during a morning blood draw for clinical labs after polysomnography; it was determined to be unrelated to LXB