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Changes in Self-Reported Cognitive Complaints, Functional Impairments, Work Productivity, and Symptom Severity in Participants With Narcolepsy After Treatment With Greater Than 9 Gram Dosages of Low-Sodium Oxybate in the DUET Study

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Objective

- To evaluate the impact of LXB dosages >9 g/night (compared with a 9 g/night dosage) on cognitive complaints, functional impairments, work productivity, and symptom severity in participants with narcolepsy

Conclusions

- Participants with narcolepsy who were identified by investigators as likely to benefit from continued titration to an optimized LXB dosage above 9 g/night experienced additional symptom benefits compared with baseline LXB 9 g/night
- Data show meaningful improvement in symptom severity, overall disease burden, cognitive complaints and related functional impacts, work productivity, and daily activities in participants titrated to optimized LXB >9 g to 12 g/night
- DUET fills an important knowledge gap by assessing LXB dosages >9 g/night and changes in the burden of disease in people with narcolepsy after LXB treatment, thereby providing insight into the benefit 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.** Harel BT, et al. *Sleep Adv.* 2024;5(1):zpae043. **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.** 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. **7.** Chasens ER, et al. *Sleep.* 2009;32(7):915-919. **8.** Masoli K, et al. *J Clin Sleep Med.* 2021;17(9):1895-1945.

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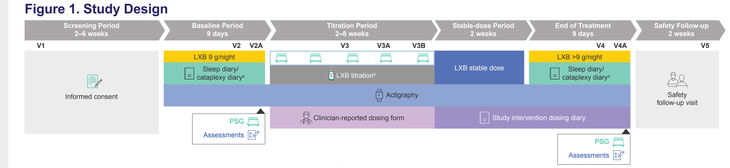
Introduction

- Narcolepsy is a central disorder of hypersomnolence associated with cognitive impairments and debilitating consequences, including impaired daily functioning, decreased work productivity, and reduced quality of life[1-3]
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat excessive daytime sleepiness (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 in the prescribing label and have not been studied extensively; however, 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]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a prospective, open-label study (NCT05875974) of LXB treatment in participants with narcolepsy (type 1 [NT1] or type 2 [NT2]) or idiopathic hypersomnia
  - DUET included a >9 g cohort of participants with narcolepsy currently taking 9 g of LXB and, in the opinion of the investigator, would likely benefit from continued titration

Methods

Figure 1. Study Design



*Cataplexy diary in narcolepsy type 1 only. †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.

- The 9-day baseline period on LXB 9 g/night ("LXB 9 g") and 9-day end-of-treatment period on an optimized stable dose of LXB ("optimized LXB >9 g") included 8 days of daily assessments ending with overnight ad libitum polysomnography and additional assessments
- Upon study entry, participants gradually titrated from 9 g to an optimized dosage up to 12 g (twice nightly; maximum of 7.5 g for first dose and 4.5 g for the second dose) with enhanced safety monitoring at each dose escalation titration step

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 were conducted in the sleep laboratory clinic with PSG and appropriate in-clinic safety monitoring
- Each dose-escalation step during titration was limited to 0.5 g/night per 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.

- Outcomes were evaluated between LXB 9 g (BL) and optimized LXB >9 g (EOT), including Patient Global Impression of Severity (PGI-S) for overall disease, Patient Global Impression of Change (PGI-C) for overall disease, and British Columbia Cognitive Complaints Inventory (BC-CCI), Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), and Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP [narcolepsy])
- Additional study details, including more information on the assessments, can be found in the Supplement, accessed via the QR code at the bottom of the poster

Results

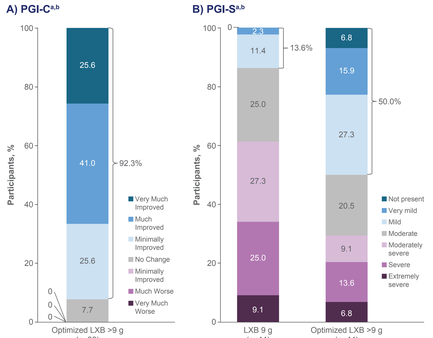
Table 1. Demographics and Baseline Characteristics[a]

Characteristic	Total >9 g Cohort (N=48)
Age, years	
Mean (SD)	39.2 (10.9)
Median (min, max)	38.0 (18, 65)
BMI (kg/m^2), mean (SD)	29.9 (8.9)
Narcolepsy type, n (%)	
NT1	18 (37.5)
NT2	30 (62.5)
Sex at birth, n (%)	
Male	30 (62.5)
Female	18 (37.5)
Race, n (%)	
White	1 (2.1)
Black or African American	7 (14.6)
Asian	1 (2.1)
Multiple[b]	37 (77.1)
Ethnicity, n (%)	
Hispanic or Latino	1 (2.1)
Not Hispanic or Latino	47 (97.9)
Comorbid OSA,[c] n (%)	
OSA	15 (31.3)
No OSA	33 (68.8)
Concomitant alerting agent use,[d] n (%)	
Alerting agent use	28 (58.3)
No alerting agent use	20 (41.7)

Proportions may not equal 100% due to rounding.
[a]Safety analysis set. [b]Participant reported >1 race. [c]Based on medical history and treatment records at screening and/or technical notes from any PSG visit where 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.
BMI, body mass index; LXB, low-sodium oxybate; max, maximum; min, minimum; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OSA, obstructive sleep apnea; SD, standard deviation.

- Most participants were female (63%) and White (77%)
- Mean (SE) nightly LXB dosage during the stable-dose period (n=45) was 11.1 (1.0) g/night
- Of those who achieved a stable dose (n=45), 46.7% (n=21) reached a stable LXB dosage of 12 g/night (the highest possible dosage; 7.5 g first dose, 4.5 g second dose)
  - Of those who reached a stable LXB dosage of 12 g/night, 71.4% (n=15) were on alerting agents and 28.6% (n=6) were not on alerting agents

Figure 2. Overall Narcolepsy Disease Improved With LXB Optimization to >9 g/Night



[a]Completer analysis set. [b]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
LXB, low-sodium oxybate; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

- When LXB was optimized to >9 g/night, most (92.3%) participants reported improvement in their overall narcolepsy disease on the PGI-C, and no participants reported that their disease worsened
- Half (50.0%) of participants rated their overall disease as "mild" to "not present" ("mild," "very mild," or "not present") on the PGI-S when LXB was optimized to >9 g/night, compared with only 13.6% at LXB 9 g/night

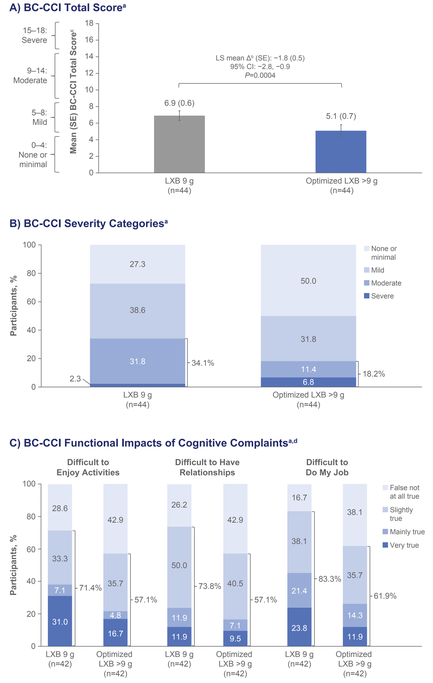
Table 2. Treatment-Emergent Adverse Events[a]

TEAEs occurring in ≥5% of participants, n (%)	Total >9 g Cohort (N=48)
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; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

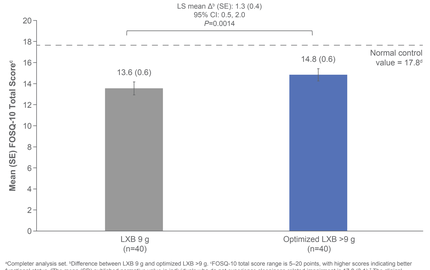
Figure 3. Cognitive Function Improved With LXB Optimization to >9 g/Night



[a]Completer analysis set. [c]Difference between LXB 9 g and optimized LXB >9 g. [d]BC-CCI total score range is 0–18, with higher scores indicating greater severity of cognitive impairment. †BC-CCI supplemental items.
BC-CCI, British Columbia Cognitive Complaints Inventory; CI, confidence interval; LS, least squares; LXB, low-sodium oxybate; SE, standard error.

- When LXB 9 g/night was increased to an optimized dosage >9 g/night, the BC-CCI total score decreased, indicating fewer and/or less severe cognitive complaints
- Half (50.0%) of participants reported "none or minimal" cognitive complaints when LXB was optimized to >9 g/night, compared with 27.3% at LXB 9 g/night
- Similarly, more participants reported fewer cognitive symptom impacts on work, relationships, or activities when LXB was optimized to >9 g/night, such that 38.1% to 42.9% endorsed "false not true at all" at optimized LXB >9 g/night compared with only 16.7% to 28.6% at LXB 9 g/night

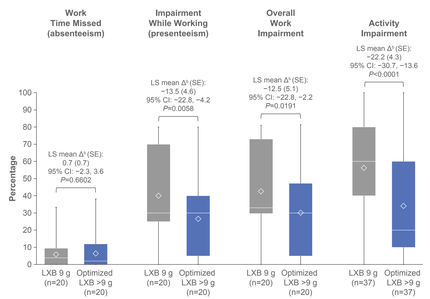
Figure 4. Participants Reported Improvement in Functioning (FOSQ-10)[a] with LXB Optimization to >9 g/Night



[a]Completer analysis set. [c]Difference between LXB 9 g and optimized LXB >9 g. [b]FOSQ-10 total score range is 5–20 points, with higher scores indicating better functional status. [a]The mean (SD) published normative value in individuals who do not experience sleepiness-related impairment is 17.8 (3.1).[1] The clinical significance threshold is 1 point.[4]
CI, confidence interval; FOSQ, Functional Outcomes of Sleep Questionnaire; LS, least squares; LXB, low-sodium oxybate; SD, standard deviation; SE, standard error.

- When LXB 9 g/night was increased to an optimized dosage >9 g/night, the FOSQ-10 total score increased (*P*=0.0014) beyond the threshold for clinically significant improvement (>1 point), indicating improved overall daily function

Figure 5. Work and Daily Activity Functioning (WPAI:SHP[a]) Improved With LXB Optimization to >9 g/night[a]



The bottom and top edges of the box indicate the first and third quartiles, the line inside the box is the median, and the diamond marker inside the box is the mean. The whiskers extending from the box indicate the minimum and maximum.
[a]Completer analysis set. [c]Difference between LXB 9 g and optimized LXB >9 g.
CI, confidence interval; LS, least squares; LXB, low-sodium oxybate; SE, standard error; WPAI:SHP, Work Productivity and Activity Impairment: Specific Health Problem.

- Compared with LXB 9 g/night, participants taking an optimized LXB >9 g dosage reported lower impairment while working (presenteeism; *P*=0.0058), lower overall work impairment (absenteeism + presenteeism; *P*=0.0191), as well as lower activity impairment (regular daily activities other than work; *P*<0.0001) due to narcolepsy

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[1]Stanford Sleep Medicine Center, Redwood City, CA, USA; [2]Mayo Clinic, Scottsdale, AZ, USA; [3]Department of Psychiatry, University of Wisconsin–Madison, Madison, WI, USA; [4]Comprehensive Sleep Medicine Associates, Houston, TX, USA; [5]Sleep Education Consortium, Sugar Land, TX, USA; [6]Jazz Pharmaceuticals, Palo Alto, CA, USA; [7]Jazz Pharmaceuticals, Philadelphia, PA, USA; [8]University of South Carolina School of Medicine, Columbia, SC, USA

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Supplemental Methods

- Participants could enter the >9 g narcolepsy cohort 1 of 2 ways:
  1) *direct enrollment* (participants taking low-sodium oxybate [LXB] 9 g/night at screening), or
  2) *transfer* (participants already enrolled in the narcolepsy cohort and had titrated up to LXB 9 g/night) if, in the opinion of the investigator, the participant would likely benefit from continued titration

Supplemental Figure 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults aged 18–75 with a primary diagnosis of NT1 or NT2[a]
- Stable use of concomitant anticataplectics or alerting agents[b] allowed
- On 9 g of LXB at screening and, in the opinion of the investigator, would likely benefit from continued titration

Exclusion Criteria

- Untreated or inadequately treated OSA at baseline PSG (AHI >10)[c]
  - 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:
  - Unstable or clinically significant medical condition
  - Behavioral, psychiatric, neurologic disorder[d]

[a]Meeting the *International Classification of Sleep Disorders–Third Edition* or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria. [b]Alerting agents (stimulants or wake-promoting agents); must be on stable dosage for ≥1 month before screening visit 1 with no plan to adjust the dosage during the study. [c]Defined as AHI >10, with hypopnea definition including a ≥4% desaturation as per *The AASM Manual for the Scoring of Sleep and Associated Events*.[1] [d]That might affect participant's safety and/or interfere with study conduct as determined by the investigator.

1. 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.

AHI, apnea-hypopnea index; AASM, American Academy of Sleep Medicine; LXB, low-sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OSA, obstructive sleep apnea; PSG, polysomnography.

- No Epworth Sleepiness Scale (ESS) score eligibility requirement was specified at screening for the >9 g cohort (transfer participants met inclusion criteria of ESS >10 when enrolled into the main cohort before transferring)
- Study populations:
  - The safety analysis set included all participants who enrolled in the study and took their prescribed LXB regimen for ≥1 night after the LXB 9 g period (N=48)
  - The completer analysis set included all participants who enrolled in the study, took their prescribed LXB regimen for ≥1 night after the LXB 9 g period, completed the stable-dose period, and completed the optimized LXB >9 g polysomnography visit (n=44)
- Observed values and change from LXB 9 g were summarized as categorical (PGI-S, PGI-C, BC-CCI severity, BC-CCI supplemental) or continuous (BC-CCI total score, FOSQ-10, WPAI:SHP) variables; no formal hypothesis testing was planned for the >9 g cohort
  - Least-squares mean differences were calculated using a mixed model with repeated measures of change from LXB 9 g to optimized LXB >9 g, adjusted for the LXB 9 g value
- During titration (dosage escalation), mean (SD) number of safety polysomnographies conducted for each participant was 4.5 (1.7) (median, 5.0; min, 1; max, 6)

Supplemental Table 1. Self-Reported Assessments and Rating Scales

Assessment	Description	Scoring
PGI-C and PGI-S	Assessment of participant's impression of response to treatment by rating their impression of change (PGI-C) or level of severity (PGI-S) for overall symptoms, sleep inertia, and fatigue	Scored using a 7-point Likert scale for each item; scoring is as follows: 1 ["very much improved"] to 7 ["very much worse"] for PGI-C and 1 ["not present"] to 7 ["extremely severe"] for PGI-S
BC-CCI[1]	Assessment of cognitive complaints (problems with concentration, memory, trouble expressing thoughts, word finding, slow thinking, and difficulty solving problems[a]); 6-item measure	Scored using a 4-point scale for each item (0 ["not at all"] to 3 ["very much"]), with a total score range of 0 to 18 (higher scores indicate more cognitive impairment); categorical scoring is as follows: 0–4, none or minimal; 5–8, mild; 9–14, moderate; 15–18, severe
FOSQ-10[2]	Assessment of the impact of daytime sleepiness on activities of daily living (daily functioning), measuring general productivity, activity level, vigilance, and intimacy and sexual relationships; 10-item measure	Participants are asked to rate the level of difficulty in completing an activity using a 4-point Likert scale for each item (1 ["yes, extreme"] to 4 ["no"]), with a total score range of 5 to 20 (higher scores indicate better daily functioning); normal control value = 17.8
WPAI:SHP[b,3]	Measures the effect of a specified health problem (ie, idiopathic hypersomnia) on work productivity and non-work activities; 6-item questionnaire	Work time missed (absenteeism), impairment while working (presenteeism), overall work impairment (absenteeism + presenteeism), and impairment in regular daily activities other than work are each expressed as a percentage (0–100%); higher percentages indicate greater reduction in productivity

[a]Three additional items that asked about how these symptoms impact work, relationships, and social/recreational activities were also included. [b]Items regarding work productivity were completed by employed participants only.

1. Iverson GL, Lam RW. *Ann Clin Psychiatry*. 2013;25(2):135-140. **2.** Chasens ER, et al. *Sleep*. 2009;32(7):915-919. **3.** Reilly MC, et al. *PharmacoEconomics*. 1993;4(5):353-365.

BC-CCI, British Columbia Cognitive Complaints Inventory; FOSQ, Functional Outcomes of Sleep Questionnaire; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.