002 Self-Reported Cognitive Complaints and Work Productivity in Participants With Narcolepsy or Idiopathic Hypersomnia After Low-Sodium Oxybate Treatment: Results From the Phase 4 DUET Study

DUET STUDY 407

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Introduction

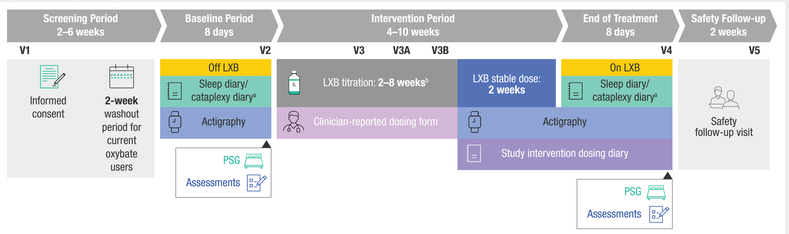
- Low-sodium oxybate (LXB; calcium, magnesium, potassium, and sodium oxybates; Xywav®) is approved by the US Food and Drug Administration for treating excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy and idiopathic hypersomnia in adults[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, multicenter, single-arm, open-label, multiple-cohort study (NCT05875974) evaluating the effectiveness of LXB on daytime and nighttime symptoms and functional outcomes in participants with narcolepsy or idiopathic hypersomnia
- Both narcolepsy and idiopathic hypersomnia are associated with impairments in cognition, attention, and work and general activity[5-7]
- The British Columbia Cognitive Complaints Inventory (BC-CCI) was developed to measure cognitive complaints in individuals with major depressive disorder[8]
  - In real-world and clinical studies, the BC-CCI has been used to assess cognitive impairment in narcolepsy[9] and idiopathic hypersomnia[10]
- The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) measures work time missed and work and activity impairment because of a specified health problem[11]
  - In a pivotal, phase 3, multicenter, placebo-controlled, double-blind, randomized withdrawal study, LXB improved work and activity impairment in adults with idiopathic hypersomnia, as assessed using the WPAI:SHP[12]

Objective

- This analysis evaluated the association of LXB with cognitive impairment, work productivity, and daily activities in participants with narcolepsy or idiopathic hypersomnia in the DUET study

Methods

Figure 1. Study Design

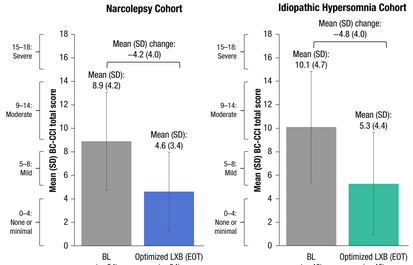


[a]Narcolepsy type 1 only.
[b]Weekly titration visits were by teleconference. Visit 3 occurred on titration day 14. Titration could take between 2 and 8 weeks. Additional in-clinic visits were scheduled for day 35 (visit 3A) and day 56 (visit 3B). Clinician could optimize participant dose and move to SDP at visit 3, 3A, or 3B, but not during intervening weekly teleconferences.
LXB, low-sodium oxybate; PSG, polysomnography; V, visit.

- DUET comprised a screening period (2-week washout for current oxybate users), an 8-day baseline (BL) period (ending with an overnight BL polysomnography [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 are taking their optimized stable dose of LXB (ending with an overnight EOT PSG with additional assessments), an optional pharmacokinetic visit (following V4 EOT; narcolepsy only), and a 2-week safety follow-up
  - **Narcolepsy cohort:** participants took LXB twice nightly (per the US prescribing label)[1]
  - **Idiopathic hypersomnia cohort:** participants took LXB once or twice nightly based on the investigator's discretion (per the US prescribing label)[1]
- Inclusion criteria included the following:
  - Eligible participants were adults (18–75 years of age, inclusive) with a primary diagnosis of narcolepsy type 1 or type 2 (*International Classification of Sleep Disorders – Third Edition* [ICSD-3] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria)[13,14] or a primary diagnosis of idiopathic hypersomnia (ICSD-3 criteria)[13]
  - Participants were required to have an Epworth Sleepiness Scale (ESS) score >10 at screening visit 1 or have an ESS score >10 at the BL PSG visit after the oxybate washout period
  - Participants were allowed to continue taking alerting agents (eg, stimulants, wake-promoting agents, or antidepressants with alerting properties) and/or concomitant anticataplectics if taking the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study period
- Exclusion criteria included the following:
  - Untreated/inadequately treated sleep-disordered breathing (ie, apnea-hypopnea index >10, with hypopnea definition including a ≥4% desaturation as per the *The AASM Manual for the Scoring of Sleep and Associated Events*),[15] as assessed during the BL PSG visit
  - History/presence of an unstable or clinically significant medical condition, behavioral/psychiatric disorder (including active suicidal ideation or current or past [within 1 year] major depressive episode)
  - History/presence of another neurologic disorder or surgical history that might affect participant's safety or interfere with study conduct, based on investigator's judgment
- The BC-CCI and WPAI:SHP, both exploratory outcomes, were administered at BL and EOT
  - The BC-CCI, a 6-item self-report measure, rates problems with concentration, memory, trouble expressing thoughts, word finding, slow thinking, and difficulty solving problems; it is 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) and categorical scoring as follows: 0–4, none or minimal cognitive complaints; 5–8, mild cognitive complaints; 9–14, moderate cognitive complaints; 15–18, severe cognitive complaints)[8]
    - Three additional items that asked about how these symptoms impact work, relationships, and social/recreational activities were also included
  - The WPAI measures work time missed (absenteeism; scored as percentage of work time missed from scheduled work hours), impairment while working (presenteeism; scored as percentage productivity at work on work days), overall work impairment (absenteeism + presenteeism), and impairment in regular daily activities other than work due to a specified health problem (in this case, narcolepsy or idiopathic hypersomnia)[11]
    - Items regarding work productivity were completed by employed participants only
- 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 (narcolepsy cohort: N=55; idiopathic hypersomnia cohort: N=46); 13 participants in the narcolepsy cohort transferred to a different study cohort; 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 visit 4 PSG EOT visit (narcolepsy cohort: n=34; idiopathic hypersomnia cohort: n=40)
- Descriptive statistics are provided for these exploratory outcomes; no inferential statistical testing was performed

Results

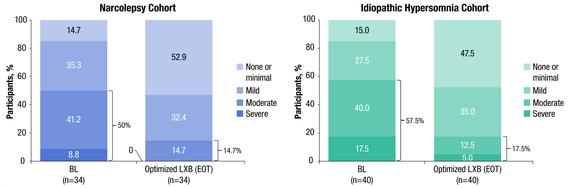
Figure 2. BC-CCI Total Score[a]



[a]Completer set.
BC-CCI, British Columbia Cognitive Complaints Inventory; BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate; SD, standard deviation.

- Participants reported improvement in their overall cognitive function, as assessed by the BC-CCI
- From BL to EOT, mean BC-CCI total score decreased from the "moderate cognitive complaints" category (9–14) to the "mild cognitive complaints" category (5–8) in participants with narcolepsy or idiopathic hypersomnia

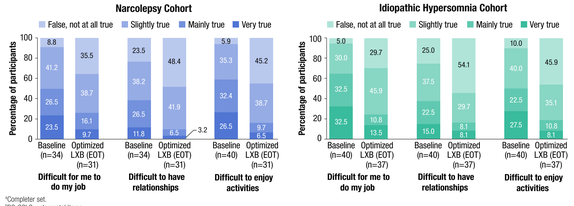
Figure 3. BC-CCI Severity Categories[a]



[a]Completer set.
BC-CCI, British Columbia Cognitive Complaints Inventory; BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate.

- Participants reported a reduction in the severity of their cognitive complaints, as assessed by the BC-CCI
- In the narcolepsy cohort, at BL, 50% of participants reported having moderate to severe cognitive complaints; at EOT, this proportion decreased to 14.7%
- In the idiopathic hypersomnia cohort, at BL, 57.5% of participants reported having moderate to severe cognitive complaints; at EOT, this proportion decreased to 17.5%

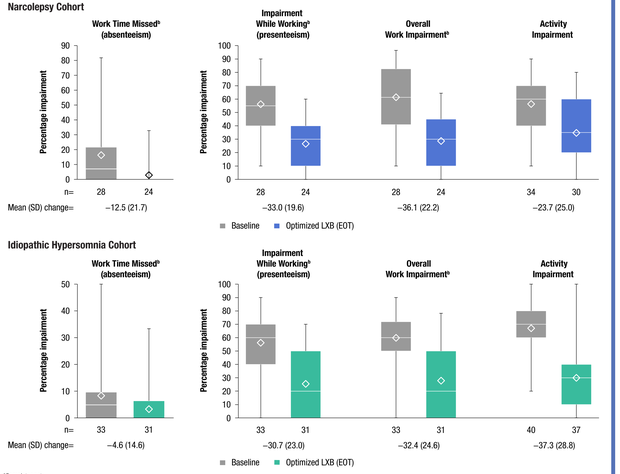
Figure 4. BC-CCI Functional Impacts of Cognitive Complaints[a,b]



[a]Completer set.
[b]BC-CCI Supplemental Items.
BC-CCI, British Columbia Cognitive Complaints Inventory; BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate.

- From BL to EOT, the proportion of participants reporting that cognitive symptoms made it difficult to work, have relationships, or enjoy activities decreased in both the narcolepsy cohort and the idiopathic hypersomnia cohort

Figure 5. WPAI:SHP Ratings of Work Productivity and Activity Impairment Due to Narcolepsy or Idiopathic Hypersomnia at BL and EOT[a]



[a]Completer set.
[b]Items pertaining to work impairment were completed by employed participants only.
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.
BL, baseline; EOT, end of treatment; SD, standard deviation; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

- At BL, absenteeism (missed work time) was high for participants with narcolepsy (mean [SD] % impairment, 16.4 [22.6]) or idiopathic hypersomnia (8.2 [12.1]); after LXB treatment, absenteeism reduced to 2.8 (7.4) and 4.5 (9.5), respectively
- Likewise, study participants had reductions in presenteeism (% impairment while working) and overall work impairment (absenteeism + presenteeism) due to narcolepsy or idiopathic hypersomnia, as well as reduced activity impairment (overall activity, not just work)

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

Characteristic	Narcolepsy Cohort (N=55)	Idiopathic Hypersomnia Cohort (N=46)
Age (years)		
Mean (SD)	33.4 (12.9)	38.1 (11.8)
Median (min, max)	29.0 (18.0, 75.0)	37.5 (20.0, 68.0)
Sex at birth, n (%)		
Male	15 (27.3)	9 (19.6)
Female	40 (72.7)	37 (80.4)
Gender identity, n (%)		
Male (including transgender man)	15 (27.3)	10 (21.7)
Female (including transgender woman)	40 (72.7)	36 (78.3)
Nonbinary	0	0
Other	0	0
Declined to state	0	0
Participant of childbearing potential, n (%)	33 (82.5)	27 (73.0)
Race, n (%)		
White	44 (80.0)	39 (84.8)
Black or African American	7 (12.7)	3 (6.5)
American Indian or Alaska Native	0	0
Asian	2 (3.6)	2 (4.3)
Native Hawaiian or other Pacific Islander	0	1 (2.2)
Multiple[b]	1 (1.8)	1 (2.2)
Unknown	1 (1.8)	0
Ethnicity, n (%)		
Hispanic or Latino	3 (5.5)	10 (21.7)
Not Hispanic or Latino	52 (94.5)	35 (76.1)
Body mass index (kg/m²)		
Mean (SD)	29.5 (6.7)	28.5 (6.4)
Median (min, max)	27.5 (20.0, 44.1)	28.2 (17.1, 45.1)
Oxybate type at study entry		
Naive[c]	42 (76.4)	37 (80.4)
Low-sodium oxybate	6 (10.9)	9 (19.6)
Sodium oxybate	5 (9.1)	0
Once-nightly sodium oxybate	2 (3.6)	0

[a]Safety set.
[b]Participant reported >1 race.
[c]No oxybate use within 2 weeks of entering the study.
BL, baseline; LXB, low-sodium oxybate; max, maximum; min, minimum; SD, standard deviation.

Table 2. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Narcolepsy Cohort (N=55)	Idiopathic Hypersomnia Cohort (N=46)
Participants with ≥1 TEAE	34 (61.8)	34 (73.9)
TEAEs occurring in ≥5% of participants in either cohort		
Nausea	12 (21.8)	9 (19.6)
Dizziness	8 (14.5)	8 (17.4)
Headache	7 (12.7)	8 (17.4)
Vomiting	6 (10.9)	5 (10.9)
Somnolence	6 (10.9)	3 (6.5)
Anxiety	4 (7.3)	3 (6.5)
Nasal congestion	4 (7.3)	2 (4.3)
Oropharyngeal pain	4 (7.3)	0
Brain fog	3 (5.5)	1 (2.2)
Decreased appetite	3 (5.5)	3 (6.5)
Enuresis	3 (5.5)	3 (6.5)
Cough	3 (5.5)	2 (4.3)
Hypoesthesia	3 (5.5)	1 (2.2)
Middle insomnia	2 (3.6)	4 (8.7)

[a]Safety set.
BL, baseline; LXB, low-sodium oxybate; TEAE, treatment-emergent adverse event.

- There were no serious AEs in the narcolepsy cohort and 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

- Participants with narcolepsy or idiopathic hypersomnia taking open-label LXB showed improvements in cognitive complaints and related functional impacts, work productivity, and daily activities
  - Reductions in moderate to severe cognitive complaints and absenteeism were substantial
- DUET is the first study to assess changes in cognitive function in people with narcolepsy or idiopathic hypersomnia following treatment with LXB
- Findings related to work productivity and daily activities in the idiopathic hypersomnia cohort are consistent with the results of the pivotal phase 3 study of LXB in idiopathic hypersomnia, which also used the WPAI:SHP assessment[12]
- Limitations of this study include the open-label and single-arm design; causality cannot be established
- Treatment-emergent adverse events were consistent with the known safety profile of LXB
- Clinicians may consider cognitive and work-related impacts when treating narcolepsy and idiopathic hypersomnia

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.** Harel BT, et al. *Sleep Adv.* 2024;5(1):zpae043. **6.** Bassi C, et al. *J Sleep Res.* 2024;33(3):e14087. **7.** Rosenberg R, et al. *J Clin Sleep Med.* 2024;20(4):643-651. **8.** Iverson GL, Lam RW. *Ann Clin Psychiatry.* 2013;25(2):135-140. **9.** Bae CJ, et al. *Sleep Med.* 2023;109:65-74. **10.** Stevens J, et al. *Nat Sci Sleep.* 2023;15:593-606. **11.** Reilly MC, et al. *Pharmacoeconomics.* 1993;4(5):353-365. **12.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **13.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **14.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013. **15.** 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.

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