Changes in Functional Status, Work Productivity, and Daily Activities in People With Idiopathic Hypersomnia and Narcolepsy Treated With Low-Sodium Oxybate: Results From the Phase 4 DUET Study

DUET STUDY 407

PCR3

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Introduction

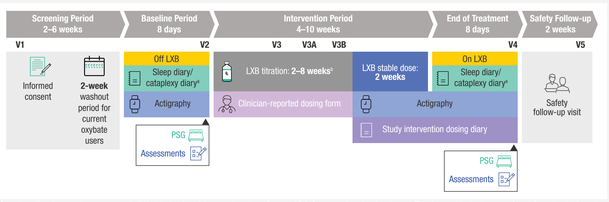
- Low-sodium oxybate (LXB; Xywav®) is approved by the US Food and Drug Administration to treat idiopathic hypersomnia in adults and excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, multicenter, single-arm, multiple-cohort, open-label study (NCT05875974)
- This patient-centric study evaluated the effectiveness of LXB on daytime and nighttime symptoms and functional outcomes in participants with idiopathic hypersomnia or narcolepsy (type 1 or type 2)

Objective

- To evaluate the effectiveness of LXB on daily functioning (measured by Functional Outcomes of Sleep Questionnaire-10 [FOSQ-10]) and on work and daily activities (measured by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem [WPAI:SHP])

Methods

Figure 1. 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 SDP at visit 3, 3A, or 3B, but not during intervening weekly teleconferences.
LXB, low-sodium oxybate; PSG, polysomnography; SDP, stable-dose period; V, visit.

- DUET included a screening period (with a 2-week washout for 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), and a 2-week safety follow-up
  - Investigators had the option of dosing LXB once- or twice-nightly for participants with idiopathic hypersomnia and twice-nightly for participants with narcolepsy (per the US prescribing label)[1]
- Participants were 18 to 75 years of age with a primary diagnosis of idiopathic hypersomnia (*International Classification of Sleep Disorders – Third Edition*[5] [ICSD-3]) or narcolepsy (ICSD-3[6] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria[7])
- Participants were required to have an Epworth Sleepiness Scale (ESS) score >10 (above the normal daytime sleepiness range[8] of ≤10) at either screening visit 1 or the BL PSG visit after the washout period, if taking an oxybate medication at entry
- Participants were allowed to continue taking concomitant anticataplectics (narcolepsy cohort only) or 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
- Exclusion criteria
  - Untreated or inadequately treated sleep-disordered breathing (ie, apnea-hypopnea index >10, with hypopnea definition including a ≥4% desaturation as per *The AASM Manual for the Scoring of Sleep and Associated Events*),[9] as assessed during the BL PSG visit
  - History/presence of an unstable or clinically significant medical condition; a behavioral/psychiatric disorder (including active suicidal ideation or a current or past [within 1 year] major depressive episode), or another neurologic disorder or surgical history that could affect the participant's safety or interfere with study conduct, as determined by the investigator
- Exploratory endpoints
  - FOSQ-10 (administered at BL and EOT)
    - Assesses the impact of sleepiness on the ability to perform daily activities
    - 10 items assessed on a Likert scale; higher scores indicate better daily functioning, with a total score range of 5 to 20 (mean among normal controls = 17.8)[10]
  - WPAI:SHP (administered at BL and EOT)
    - Assesses the effect of a specific health problem (idiopathic hypersomnia or narcolepsy) on the ability to work and perform regular activities
    - 6-item questionnaire with 4 outcomes: percentage of work time missed (absenteeism), difficulty performing tasks while at work (presenteeism; percentage of impairment), overall work impairment (absenteeism + presenteeism), and activity impairment (percentage of impairment of regular daily activities outside of work)[11]
    - Work-related questions were only asked of employed participants; everyone responded to the item regarding overall activity
- 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 (idiopathic hypersomnia: N=46; narcolepsy: N=55); 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 PSG EOT visit (idiopathic hypersomnia: n=40; narcolepsy cohort: n=34)
- *P* values in this analysis were not controlled for multiplicity and were considered nominal

Results

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

Characteristic	Idiopathic Hypersomnia (N=46)	Narcolepsy (N=55)
Age (years)		
Mean (SD)	38.1 (11.8)	33.4 (12.9)
Median (min, max)	37.5 (20.0, 68.0)	29.0 (18.0, 75.0)
Sex at birth, n (%)		
Male	9 (19.6)	15 (27.3)
Female	37 (80.4)	40 (72.7)
Gender identity, n (%)		
Male (including transgender man)	10 (21.7)	15 (27.3)
Female (including transgender woman)	36 (78.3)	40 (72.7)
Nonbinary	0	0
Other	0	0
Declined to state	0	0
Participant of childbearing potential, n (%)	27 (73.0)	33 (82.5)
Race, n (%)		
White	39 (84.8)	44 (80.0)
Black or African American	3 (6.5)	7 (12.7)
American Indian or Alaska Native	0	0
Asian	2 (4.3)	2 (3.6)
Native Hawaiian or other Pacific Islander	1 (2.2)	0
Multiple[b]	1 (2.2)	1 (1.8)
Unknown	0	1 (1.8)
Ethnicity, n (%)		
Hispanic or Latino	10 (21.7)	3 (5.5)
Not Hispanic or Latino	35 (76.1)	52 (94.5)
Body mass index (kg/m²)		
Mean (SD)	28.5 (6.4)	29.5 (6.7)
Median (min, max)	28.2 (17.1, 45.1)	27.5 (20.0, 44.1)
Oxybate type at study entry[c], n (%)		
Naive[d]	37 (80.4)	42 (76.4)
Low-sodium oxybate	9 (19.6)	6 (10.9)
Sodium oxybate	0	5 (9.1)
Once-nightly sodium oxybate	0	2 (3.6)
Oxybate total nightly dosage at screening[e] (g)		
Mean (SD)	6.8 (2.2)	7.4 (1.4)
Median (min, max)	6.8 (3.8, 9.0)	7.0 (5.6, 9.0)

[a]Safety analysis set. [b]Participant reported >1 race. [c]13 participants with narcolepsy and 9 with idiopathic hypersomnia were taking oxybate at study entry prior to washout. [d]No oxybate use within 2 weeks of entering the study. [e]For the 9 participants with idiopathic hypersomnia and 13 with narcolepsy who were taking an oxybate at screening and prior to washout.
BL, baseline; LXB, low-sodium oxybate; max, maximum; min, minimum; SD, standard deviation.

- Forty-six participants with idiopathic hypersomnia and 55 with narcolepsy were enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period
  - Most were female (80.4% idiopathic hypersomnia cohort; 72.7% narcolepsy cohort) and White (84.8% idiopathic hypersomnia cohort; 80.0% narcolepsy cohort)

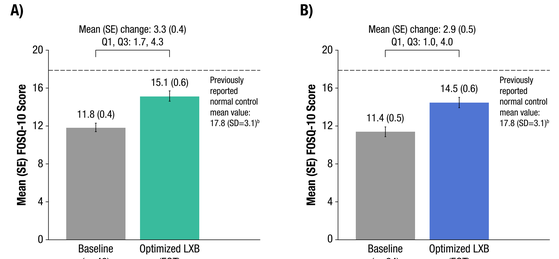
Table 2. Concomitant Alerting and Anticataplectic Medications for Enrolled Participants[a]

Preferred Term, n (%)	Idiopathic Hypersomnia (N=46)	Narcolepsy (N=55)
Participants taking a concomitant alerting agent[b,c,d]	19 (41.3)	31 (56.4)
Centrally acting antiobesity products		
Benzphetamine	1 (2.2)	0
Phentermine	1 (2.2)	0
Centrally acting sympathomimetics		
Amphetamine aspartate, amphetamine sulfate, dexamphetamine saccharate, dexamphetamine sulfate	8 (17.4)	14 (25.5)
Solriamfetol hydrochloride	5 (10.9)	5 (9.1)
Dexamphetamine sulfate	2 (4.3)	0
Methylphenidate	2 (4.3)	5 (9.1)
Modafinil	2 (4.3)	1 (1.8)
Dexamphetamine	1 (2.2)	0
Lisdexamfetamine dimesylate	0	4 (7.3)
Armodafinil	0	1 (1.8)
Dexmethylphenidate hydrochloride	0	1 (1.8)
Other antidepressants		
Bupropion hydrochloride	6 (13.0)	3 (5.5)
Other nervous system drugs		
Pitolisant hydrochloride	1 (2.2)	8 (14.5)

[a]Safety analysis set. [b]Participants could have been taking multiple different alerting medications. [c]It is not known whether these agents were prescribed for excessive sleepiness, narcolepsy, idiopathic hypersomnia, or another condition. [d]Concomitant medications could have a stop date on or after date of first dose of study intervention or were ongoing.

- Nineteen (41.3%) participants in the idiopathic hypersomnia cohort and 31 (56.4%) in the narcolepsy cohort were taking alerting agents

Figure 2. Functional Outcomes of Sleep Questionnaire Scores for Participants With Idiopathic Hypersomnia (A)[a] and Narcolepsy (B)[a]



[a]Completer analysis set. [b]Higher scores indicate better daily functioning.[10] [c]Not all participants completed all assessments.
BL, baseline; EOT, end of treatment; FOSQ, Functional Outcomes of Sleep Questionnaire; LXB, low-sodium oxybate; PSG, polysomnography; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; SDP, stable-dose period; SE, standard error.

- Participants with idiopathic hypersomnia and narcolepsy taking LXB showed improvements in functional status from BL to EOT
- The mean (SE) change from BL was 3.3 (0.4) points for the idiopathic hypersomnia cohort and 2.9 (0.5) points for the narcolepsy cohort, both exceeding the minimal clinically important difference threshold of 1.7 points[12]

Table 3. Mean Nightly LXB Dosage During Stable-Dose Period

	Idiopathic Hypersomnia (n=41)[a]	Narcolepsy (n=36)[a]
Overall total nightly LXB dose, grams, mean (SD)	6.6 (1.8)	7.0 (1.6)
	Idiopathic Hypersomnia (n=26)[a]	**Narcolepsy (n=36)[a]**
Twice-nightly LXB dosage, grams, mean (SD)	7.7 (1.2)	7.0 (1.6)
First nightly LXB dose	4.0 (0.8)	3.7 (0.9)
Second nightly LXB dose	3.6 (0.8)	3.4 (0.9)
	Idiopathic Hypersomnia (n=15)[a]	
Once-nightly LXB dose,[b] grams, mean (SD)	4.8 (1.1)	NA

[a]Includes all participants from the safety set who reached the SDP. [b]Per the US prescribing information, participants with idiopathic hypersomnia were on a once- or twice-nightly regimen, whereas participants with narcolepsy were all on twice-nightly regimens.
LXB, low-sodium oxybate; NA, not applicable; 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
- The average optimized total nightly dosage was 6.6 g/night for the idiopathic hypersomnia cohort and 7.0 g/night for the narcolepsy cohort

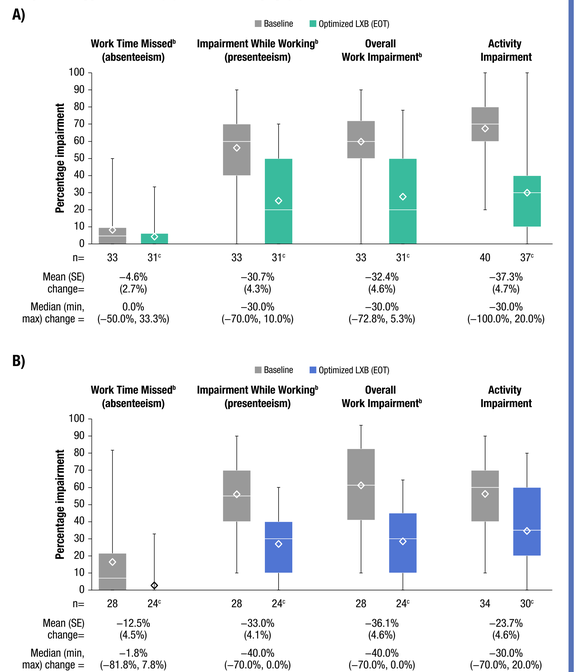
Table 4. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Idiopathic Hypersomnia (N=46)	Narcolepsy (N=55)
With ≥1 TEAE	34 (73.9)	34 (61.8)
With ≥1 TEAE related to treatment	30 (65.2)	30 (54.5)
With ≥1 serious TEAE	1 (2.2)	0
With ≥1 serious TEAE related to treatment	0	0
With ≥1 TEAE leading to discontinuation	1 (2.2)	4 (7.3)
TEAEs occurring in ≥5% of participants in either cohort		
Nausea	9 (19.6)	13 (23.6)
Dizziness	8 (17.4)	8 (14.5)
Headache	8 (17.4)	7 (12.7)
Vomiting	5 (10.9)	6 (10.9)
Somnolence	3 (6.5)	6 (10.9)
Anxiety	3 (6.5)	4 (7.3)
Nasal congestion	2 (4.3)	4 (7.3)
Oropharyngeal pain	0	4 (7.3)
Brain fog	1 (2.2)	3 (5.5)
Decreased appetite	3 (6.5)	3 (5.5)
Enuresis	3 (6.5)	3 (5.5)
Cough	2 (4.3)	3 (5.5)
Hypoesthesia	1 (2.2)	3 (5.5)
Middle insomnia	4 (8.7)	2 (3.6)

[a]Safety analysis set.
TEAE, treatment emergent adverse event.

- Thirty-four (73.9%) participants with idiopathic hypersomnia and 34 (61.8%) with narcolepsy reported a TEAE
- TEAEs were mild or moderate in severity; 1 participant with idiopathic hypersomnia and 4 with narcolepsy discontinued treatment due to a TEAE
  - TEAEs that led to discontinuation were depression (n=1) in the idiopathic hypersomnia cohort, and nausea (n=1), pregnancy (n=1), anxiety (n=1), and dysphoria and irritability (n=1) in the narcolepsy cohort
- There was 1 serious adverse event in the idiopathic hypersomnia cohort (hypoxia [concurrent with influenza], moderate severity, deemed to be unrelated to study drug by the investigator, and resolved) and no serious adverse events in the narcolepsy cohort

Figure 3. Work Productivity and Activity Impairment Scores for Participants With Idiopathic Hypersomnia (A)[a] and Narcolepsy (B)[a]



[a]Completer analysis set. [b]Items pertaining to work impairment were completed by employed participants only. [c]Not all participants completed all assessments.
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 is the mean. The whiskers extending from the box indicate the minimum and maximum.
EOT, end of treatment; LXB, low-sodium oxybate; SE, standard error.

- Participants with idiopathic hypersomnia and narcolepsy taking LXB showed improvements in work productivity and non-work–related activities from BL to EOT
  - At BL, participants in both cohorts experienced a high percentage of work time missed (absenteeism), with mean (SE) values of 8.2% (2.1%) for idiopathic hypersomnia and 16.4% (4.3%) for narcolepsy; at EOT, the percentage of work time missed (absenteeism) reduced to mean (SE) values of 4.5% (1.7%) for idiopathic hypersomnia and 2.8% (1.5%) for narcolepsy
  - Similarly, participants in both cohorts showed reductions in impairment while working (presenteeism) and overall work impairment (absenteeism + presenteeism) due to idiopathic hypersomnia or narcolepsy, as well as reduced activity impairment (overall activity, not just work)

Conclusions

- Participants with idiopathic hypersomnia and with narcolepsy taking open-label LXB demonstrated improvements in daily functioning, overall work productivity, and non–work-related activities
- This study provides prospective data on LXB treatment of idiopathic hypersomnia and narcolepsy, and provides new findings on daily functioning and work productivity through individualized optimization of LXB treatment in a clinical setting
  - Limitations of the study include the open-label and single-arm design; causality cannot be established
  - Analyses were based on the completer set of participants and may not represent the experience of all individuals starting LXB treatment
- TEAEs were consistent with the known safety profile of LXB
- These findings reinforce the established effectiveness of LXB as a treatment for idiopathic hypersomnia or narcolepsy

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. Accessed February 28, 2023. **4.** US Food and Drug Administration. 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. Accessed October 11, 2022. **5.** American Academy of Sleep Medicine. Idiopathic hypersomnia. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **6.** American Academy of Sleep Medicine. Narcolepsy type 1. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **7.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* Washington, DC: American Psychiatric Publishing; 2013. **8.** Johns MW. *Sleep.* 1991;14(6):540-545. **9.** 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. **10.** Chasens ER, et al. *Sleep.* 2009;32(7):915-919. **11.** Reilly MC, et al. *Pharmacoeconomics.* 1993;4(5):353-365. **12.** Weaver TE, et al. *Sleep Breath.* 2021;25(3):1707-1715.

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