Effectiveness and Safety of Low-Sodium Oxybate in Participants With Narcolepsy: Top-line Results From the Phase 4 DUET Study

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DUET STUDY 407

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Introduction

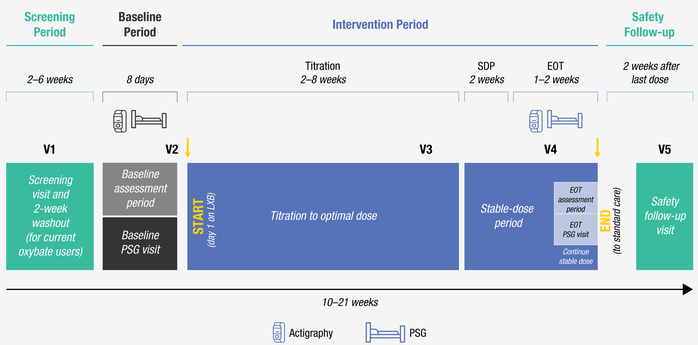
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy and idiopathic hypersomnia in adults[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) is a phase 4, prospective, multicenter, single-arm, open-label multiple-cohort study (NCT05875974)
- This patient-centric study is evaluating the effectiveness of LXB on daytime and nighttime symptoms and functional outcomes in participants with narcolepsy (type 1 [NT1] or type 2 [NT2]) or idiopathic hypersomnia
  - For results from the idiopathic hypersomnia cohort of DUET, please refer to Poster 165

Objective

- To evaluate the effectiveness and safety of LXB on EDS and sleep architecture and disruption (measured by polysomnography [PSG]) in participants with narcolepsy

Methods

Figure 1. Study Design



EOT, end of treatment; LXB, low-sodium oxybate; PK, pharmacokinetics; PSG, polysomnography; SDP, stable-dose period; V, visit.

- DUET includes a screening period (2-week washout for current oxybate users), an 8-day baseline period, a 2- to 8-week LXB titration period, a 2-week stable-dose period (SDP), a 1- to 2-week end-of-treatment period, and a 2-week safety follow-up
- Participants were 18 to 75 years of age with a primary diagnosis of NT1 or NT2 (meeting the *International Classification of Sleep Disorders – Third Edition* [ICSD-3] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria)
- Participants were required to have an Epworth Sleepiness Scale (ESS) score >10 at screening visit 1 or if currently taking an oxybate medication, have an ESS score >10 after the washout period
- Participants were allowed to continue taking concomitant anticataplectics or alerting 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 included the following:
  - Untreated/inadequately treated sleep-disordered breathing (ie, apnea-hypopnea index >10),[6] as assessed during baseline polysomnography 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 primary endpoint was change in ESS score from baseline to end of treatment. Additional statistical methods are available through the QR code in the bottom right corner of this poster
- Key secondary endpoints for the narcolepsy cohort included the following 3 PSG parameters: change in total number of shifts from deeper to lighter stages of sleep (from N1/N2/N3/rapid eye movement [REM] to wake and from N2/N3/REM to N1), stage N3 sleep duration (minutes), and number of awakenings
- 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 ≥1 dose of the study drug after the baseline period; the completer analysis set includes all participants who enrolled in the study, took ≥1 dose of the study drug after the baseline period, completed the SDP, and completed the visit 4 polysomnography end-of-treatment visit

Results

Table 1. Baseline Demographics for Enrolled Participants With Narcolepsy

Characteristic	Safety Set[a] (N=55)
Age (years)	
Mean (SD)	33.4 (12.9)
Median (min, max)	29.0 (18, 75)
Sex at birth, n (%)	
Male	15 (27.3)
Female	40 (72.7)
Gender identity, n (%)	
Male (including transgender man)	15 (27.3)
Female (including transgender woman)	40 (72.7)
Nonbinary	0
Other	0
Declined to state	0
Participant of childbearing potential, n (%)	
Yes	33 (82.5)
Race, n (%)	
White	44 (80.0)
Black or African American	7 (12.7)
American Indian or Alaska Native	0
Asian	2 (3.6)
Native Hawaiian or other Pacific Islander	0
Multiple	1 (1.8)
Ethnicity, n (%)	
Hispanic or Latino	3 (5.5)
Not Hispanic or Latino	52 (94.5)
Body mass index (kg/m²)	
Mean (SD)	29.5 (6.7)
Median (min, max)	27.5 (20, 44)
Oxybate type at study entry, n (%)	
Naive[b]	42 (76.4)
Low-sodium oxybate	6 (10.9)
Sodium oxybate	5 (9.1)
Fixed-dose sodium oxybate	2 (3.6)

[a]Safety set includes all participants who enrolled in study and took ≥1 dose of study drug after baseline period. [b]No oxybate use within 2 weeks of entering study.
max, maximum; min, minimum; SD, standard deviation.

- Fifty-five participants with narcolepsy enrolled in the study and took ≥1 dose of study drug after the baseline period; most were female (72.7%) and White (80.0%)

Table 2. Mean Nightly LXB Dose During Stable-Dose Period

Grams, mean (SD)	Safety Set[a] (N=36)
Total nightly LXB dose	7.0 (1.6)
First nightly LXB dose	3.7 (0.9)
Second nightly LXB dose	3.4 (0.9)

[a]Includes participants from the safety set who reached the stable-dose period.
LXB, low-sodium oxybate; SD, standard deviation.

- Once a participant reached a stable (optimized) dose, the total nightly LXB dose was tabulated during the SDP, which includes the EOT period

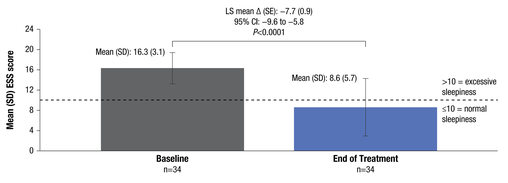
Table 3. Concomitant Alerting Medications

ATC Level 4 Term, n (%)	N=55[a,b]
Participants taking a concomitant alerting agent,[c,d] n (%)	31 (56.4)
Centrally acting sympathomimetics	
Amphetamine aspartate, amphetamine sulfate, dexamphetamine saccharate, dexamphetamine sulfate	14 (25.5)
Methylphenidate	5 (9.1)
Modafinil	5 (9.1)
Solriamfetol hydrochloride	5 (9.1)
Lisdexamphetamine mesilate	4 (7.3)
Armodafinil	3 (5.5)
Dexmethylphenidate hydrochloride	1 (1.8)
Other antidepressants	
Bupropion hydrochloride	3 (5.5)
Other nervous system drugs	
Pitolisant hydrochloride	8 (14.5)

[a]Safety set includes all participants who enrolled in study and took ≥1 dose of study drug after baseline period. [b]Participants could have been taking multiple different alerting medications. [c]It is not known whether these agents were prescribed for excessive sleepiness, narcolepsy, and/or another condition. [d]Concomitant medications had a stop date on or after date of first dose of study intervention or were ongoing.
ATC, anatomic therapeutic chemical.

- At study entry, 31 participants (56.4%) were taking alerting agents, with amphetamines being the most common (25.5%)

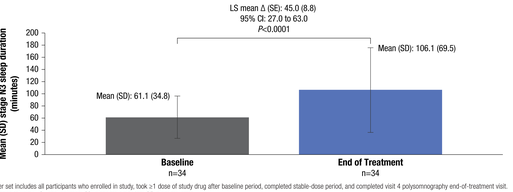
Figure 2. Epworth Sleepiness Scale Score[a]



[a]Completer set includes all participants who enrolled in study, took ≥1 dose of study drug after baseline period, completed stable-dose period, and completed visit 4 polysomnography end-of-treatment visit.
CI, confidence interval; ESS, Epworth Sleepiness Scale; LS, least squares; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB showed improvements in EDS on the ESS from baseline to end of treatment

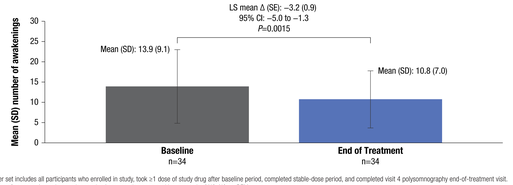
Figure 4. N3 Sleep (Deep Sleep) Duration[a]



[a]Completer set includes all participants who enrolled in study, took ≥1 dose of study drug after baseline period, completed stable-dose period, and completed visit 4 polysomnography end-of-treatment visit.
CI, confidence interval; LS, least squares; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had an increase in N3 sleep duration from baseline to end of treatment

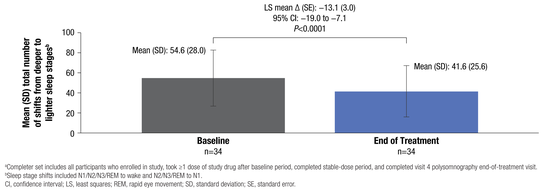
Figure 5. Number of Awakenings[a,b]



[a]Completer set includes all participants who enrolled in study, took ≥1 dose of study drug after baseline period, completed stable-dose period, and completed visit 4 polysomnography end-of-treatment visit. [b]Defined as ≥2 consecutive wake epochs; awakenings must be separated by an epoch of N2, N3, or REM.
CI, confidence interval; LS, least squares; REM, rapid eye movement; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had a reduction in the number of awakenings from baseline to end of treatment

Figure 3. Total Number of Shifts From Deeper to Lighter Stages of Sleep[a]



[a]Completer set includes all participants who enrolled in study, took ≥1 dose of study drug after baseline period, completed stable-dose period, and completed visit 4 polysomnography end-of-treatment visit.
[b]Sleep stage shifts included N1/N2/N3/REM to wake and N2/N3/REM to N1.
CI, confidence interval; LS, least squares; REM, rapid eye movement; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had a reduction in total number of shifts from deeper to lighter sleep stages from baseline to end of treatment

Table 4. Treatment-Emergent Adverse Events

Participants, n (%)	Safety Set[a] (N=55)
With ≥1 TEAE	33 (60.0)
With ≥1 TEAE related to treatment	28 (50.9)
With ≥1 serious TEAE	0
With ≥1 serious TEAE related to treatment	0
With ≥1 TEAE leading to discontinuation	4 (7.3)
TEAEs occurring in ≥5% of participants	
Nausea	11 (20.0)
Dizziness	8 (14.5)
Headache	7 (12.7)
Somnolence	6 (10.9)
Vomiting	6 (10.9)
Anxiety	4 (7.3)
Nasal congestion	4 (7.3)
Oropharyngeal pain	4 (7.3)
Brain fog	3 (5.5)
Cough	3 (5.5)
Decreased appetite	3 (5.5)
Enuresis	3 (5.5)
Hypoesthesia	3 (5.5)

[a]Safety set includes all participants who enrolled in study and took ≥1 dose of study drug after baseline period.
TEAE, treatment-emergent adverse event.

- Thirty-three participants (60.0%) reported a TEAE
- Four participants discontinued treatment due to TEAEs
  - TEAEs that led to discontinuation included nausea, pregnancy, anxiety, dysphoria, and irritability
- There were no serious TEAEs reported in this cohort

Conclusions

- This study provides prospective data on LXB treatment of EDS in narcolepsy; additionally, it offers data from PSG conducted in a real-world clinical setting with individualized optimization of LXB treatment
  - The study is limited by its open-label design and lack of a control cohort, which limits the ability to attribute the findings to LXB
- Participants with narcolepsy taking open-label LXB demonstrated reduced EDS, fewer shifts from deeper to lighter stages of sleep, increased duration of deep sleep (N3), and a decrease in the number of awakenings, which suggests a reduction in disrupted nighttime sleep
- Overall, 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.; 2023. **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 labelling 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.** Bogan RK, et al. *Sleep.* 2021;44(3):zsaa206. **6.** Berry RB, et al, for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* Version 3.0. 2023.

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Supplemental Statistical Methods

- Formal hypothesis testing was conducted using the Completer Set for the following endpoints for the narcolepsy cohort:
  1. Epworth Sleepiness Scale total score (decrease from baseline)
  2. Total sleep stage shifts from N1/N2/N3/REM to wake and N2/N3/REM to N1 (decrease from baseline)
  3. Duration of N3 sleep (increase from baseline)
  4. Total number of nocturnal awakenings (decrease from baseline)
- Decreases or increases from baseline were estimated using an analysis of covariance (ANCOVA) model adjusted for the baseline value. The parameter of interest for each endpoint, the least-squares mean difference at the end-of-treatment visit, was compared against a null hypothesis value of 0.
- Multiplicity control was achieved using a sequential testing strategy conducted separately for each cohort. Listed endpoints were tested in the order shown above. Hypothesis tests with 2-sided $P<0.05$ in the expected direction were considered statistically significant. If any ordered endpoint failed to reject the null hypothesis, subsequent hypothesis tests were considered nominal. Hypothesis tests for endpoints not included in the sequential testing procedure were considered nominal.