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

DUET STUDY 407

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Introduction

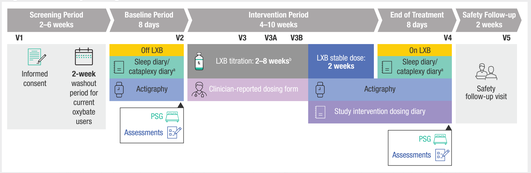
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy or idiopathic hypersomnia in adults[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating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

Objectives

- The objectives of this analysis were to evaluate the safety and effectiveness of LXB on daytime and nighttime-related symptoms

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 dosing 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 cohort 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) or a primary diagnosis of idiopathic hypersomnia (ICSD-3 criteria)
  - 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 AASM Manual for the Scoring of Sleep and Associated Events*),[5] 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 primary endpoint in both cohorts was change in ESS score from BL to EOT
- Key secondary endpoints (change from BL to EOT) included:
  - **Narcolepsy cohort:** 3 PSG parameters: change in total number of shifts from deeper to lighter stages of sleep (from N1/N2/N3/REM to wake and from N2/N3/REM to N1; from the onset of persistent sleep to lights on), stage N3 sleep duration (in minutes; from the first epoch of sleep [any stage] to lights on), and number of nocturnal awakenings (defined as ≥2 consecutive wake epochs, separated by an epoch of stage N2, N3, or REM; from lights off to lights on)
  - **Idiopathic hypersomnia cohort:** change in the Idiopathic Hypersomnia Severity Scale (IHSS) total score
- Additional secondary endpoints reported here include the Patient Global Impression of Change (PGI-C) for overall narcolepsy disease, PGI-C for overall idiopathic hypersomnia disease, and PGI-C for sleep inertia (idiopathic hypersomnia cohort)
- Safety endpoints included incidence and severity of treatment-emergent adverse events (TEAEs) (both cohorts)
- 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 PSG EOT visit (narcolepsy cohort: n=34; idiopathic hypersomnia cohort: n=40)
- Details on statistical methodology and centralized PSG scoring definitions are available through the QR code on the bottom right corner of this poster

Results

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[c]		
Naive[d]	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]Participants taking oxybate at study entry prior to washout included n=13 (narcolepsy) and n=9 (idiopathic hypersomnia). [d]No oxybate use within 2 weeks of entering the study.
max, maximum; min, minimum; SD, standard deviation.

- Fifty-five participants with narcolepsy and 46 participants with idiopathic hypersomnia enrolled in the study and took their prescribed LXB regimen after the BL period
  - Most were female (72.7% narcolepsy cohort; 80.4% idiopathic hypersomnia cohort) and White (80.0% narcolepsy cohort; 84.8% idiopathic hypersomnia cohort)

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

Grams, mean (SD)	Narcolepsy (n=36)[a]	Idiopathic Hypersomnia (n=41)[a]
Overall total nightly LXB dose	7.0 (1.6)	6.6 (1.8)
	Narcolepsy (n=35)[a]	**Idiopathic Hypersomnia (n=26)[a]**
Twice-nightly LXB dosage	7.0 (1.6)	7.7 (1.2)
First nightly LXB dose	3.7 (0.9)	4.0 (0.8)
Second nightly LXB dose	3.4 (0.9)	3.6 (0.8)
		Idiopathic Hypersomnia (n=15)[a]
Once-nightly LXB dose[b]	NA	4.8 (1.1)

[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-nightly or a 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 a stable (optimized) dosage based on clinician judgment, the total nightly LXB dosage was tabulated during the SDP, which includes the EOT period

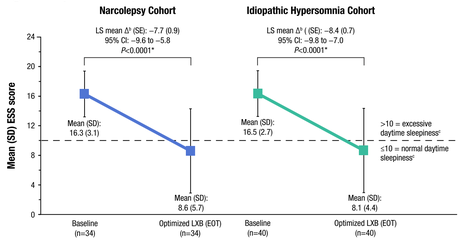
Table 3. Concomitant Alerting and Anticataplectic Medications[a,b]

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

[a]Safety 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.
ATC, anatomical therapeutic chemical.

- Thirty-one participants (56.4%) in the narcolepsy cohort and 19 (41.3%) in the idiopathic hypersomnia cohort were taking alerting agents

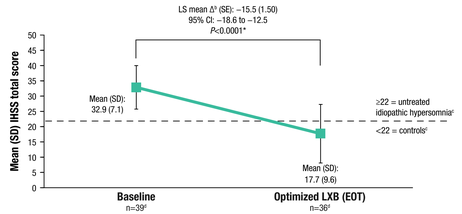
Figure 2. Epworth Sleepiness Scale Score[a]



[a]Completer set. [b]Difference between EOT and BL. [c]Mean (SD) ESS score for a normal population without a sleep disorder is 5.9 (2.2); established categories consider scores up to 10 normal.[4] An ESS score >10 at screening was required for inclusion in DUET.
*Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; SD, standard deviation; SE, standard error.

- Participants with narcolepsy or idiopathic hypersomnia taking LXB showed statistically significant reductions in mean ESS score from BL to EOT

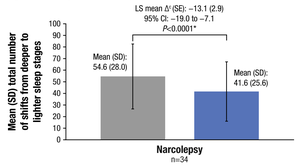
Figure 3. Idiopathic Hypersomnia Severity Scale Scores[a] (Idiopathic Hypersomnia Cohort)



[a]Completer set. [b]Difference between EOT and BL. [c]A score of 22 on the IHSS is the optimal cutoff for differentiating between untreated individuals with idiopathic hypersomnia and community-dwelling controls.[3] [d]Not all participants completed all assessments.
*Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least-squares; LXB, low-sodium oxybate; SD, standard deviation; SE, standard error.

- Participants with idiopathic hypersomnia taking LXB showed a statistically significant reduction in the IHSS from BL to EOT

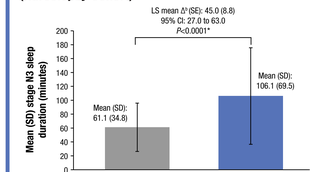
Figure 4. Total Number of Shifts From Deeper to Lighter Stages of Sleep (Narcolepsy Cohort)[a,b]



[a]Completer set. [b]Sleep stage shifts included N1/N2/N3/REM to wake and N2/N3/REM to N1. [c]Difference between EOT and BL.
*Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N1, non-REM stage 1; N2, non-REM stage 2; N3, non-REM stage 3; REM, rapid eye movement; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had a statistically significant reduction in total number of shifts from deeper to lighter sleep stages from BL to EOT

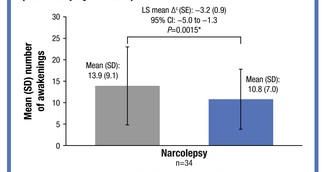
Figure 5. Stage N3 Sleep Duration (Narcolepsy Cohort)[a]



[a]Completer set. [b]Difference between EOT and BL.
*Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N3, non-REM stage 3; REM, rapid eye movement; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had a statistically significant increase in stage N3 sleep duration from BL to EOT

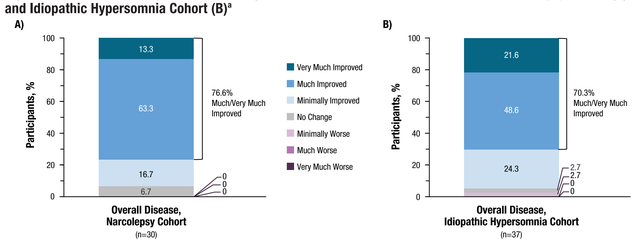
Figure 6. Number of Nocturnal Awakenings[a] (Narcolepsy Cohort)[b]



[a]Defined as ≥2 consecutive wake epochs; awakenings must have been separated by an epoch of stage N2, N3, or REM. [b]Completer set. [c]Difference between EOT and BL.
*Controlled for multiplicity.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; N2, non-REM stage 2; N3, non-REM stage 3; REM, rapid eye movement; SD, standard deviation; SE, standard error.

- Participants with narcolepsy taking LXB had a statistically significant reduction in the number of nocturnal awakenings from BL to EOT

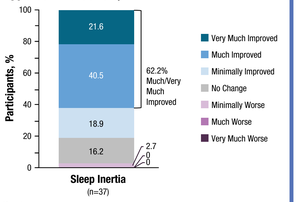
Figure 7. Patient Global Impression of Change at End of Treatment for Overall Disease: Narcolepsy Cohort (A) and Idiopathic Hypersomnia Cohort (B)[a]



[a]Completer set.

- 76.6% of participants with narcolepsy, and 70.3% of participants with idiopathic hypersomnia reported "very much" or "much" improvement on the PGI-C

Figure 8. Patient Global Impression of Change at End of Treatment for Sleep Inertia (Idiopathic Hypersomnia Cohort)[a]



[a]Completer set.

- Most participants with idiopathic hypersomnia reported "very much" or "much" improvement on the PGI-C for sleep inertia (62.2%)

Table 4. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Narcolepsy (N=55)	Idiopathic Hypersomnia (N=46)
With ≥1 TEAE	34 (61.8)	34 (73.9)
With ≥1 TEAE related to treatment	29 (52.7)	30 (65.2)
With ≥1 TEAE leading to discontinuation	4 (7.3)	1 (2.2)
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.
TEAE, treatment-emergent adverse event.

- The overall TEAE incidence was 61.8% in the narcolepsy cohort and 73.9% in the idiopathic hypersomnia cohort
- TEAEs were mild or moderate in severity; 4 participants with narcolepsy and 1 participant with idiopathic hypersomnia discontinued treatment due to a TEAE
- 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 taking open-label LXB demonstrated reduced EDS and less disrupted nighttime sleep, as demonstrated by fewer shifts from deeper to lighter stages of sleep, increased duration of deep sleep (N3), and a decrease in the number of nocturnal awakenings
- Participants with idiopathic hypersomnia taking open-label LXB demonstrated improvements in EDS and sleep inertia
- Limitations include the open-label and single-arm design; causality cannot be established
- Overall, TEAEs were consistent with the known safety profile of LXB
- These findings reinforce the burden of symptoms experienced by people living with narcolepsy and idiopathic hypersomnia, and further support LXB as an effective treatment for these disorders

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.** 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. **6.** Johns MW. *Sleep.* 1991;14(6):540-545. **7.** Dauvilliers Y, et al. *Neurology.* 2019;92(15):e1754-e1762.

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Supplemental Statistical Methods

- **Narcolepsy Cohort:** Formal hypothesis testing was conducted using the completer set for the following endpoints:
  1. Epworth Sleepiness Scale (ESS) score (decrease from baseline [BL])
  2. Total sleep stage shifts from N1/N2/N3/REM to wake and N2/N3/REM to N1 (decrease from BL)
  3. Duration of stage N3 sleep (increase from BL)
  4. Total number of nocturnal awakenings (decrease from BL)
- Decreases or increases from BL were estimated using an analysis of covariance (ANCOVA) model adjusted for the BL value. The parameter of interest for each endpoint, the least-squares mean difference at the end-of-treatment (EOT) 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. The Patient Global Impression of Change (PGI-C) endpoints were not controlled for multiplicity.
- **Idiopathic Hypersomnia Cohort:** Formal hypothesis testing was conducted in accordance with the statistical analysis plan using the completer set for the following endpoints:
  1. ESS total score (decrease from BL)
  2. Idiopathic Hypersomnia Severity Scale (IHSS) total score (decrease from BL)
- Decreases from BL for ESS and IHSS total scores were estimated using an ANCOVA model adjusted for the BL value. The parameter of interest for each endpoint, the least-squares mean difference at the EOT visit, was compared against a null hypothesis value of 0.
- Multiplicity control was achieved using a sequential testing strategy in which the ESS endpoint was tested first, followed by the IHSS endpoint. 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. PGI-C endpoints were not controlled for multiplicity.

- **Centralized Polysomnography Scoring Definitions**: The following sleep stage definitions were adapted from the American Academy of Sleep Medicine Manual for Scoring Sleep:
  - **Epoch:** a standard 30 second duration of the sleep recording that is assigned a sleep stage value.
  - **Stage W:** corresponds to the waking state ranging from full alertness through the early stages of drowsiness; characterized by alpha activity in the electroencephalogram (EEG): trains of sinusoidal 8–13 Hz activity recorded over the occipital region with eye closure, attenuating with eye opening; any epoch between Lights Off and Lights On during which a participant is out of bed is scored as Stage W.
  - **Stage N1:** a relatively low amplitude, mixed frequency (LAMF) EEG with a majority of activity in the 4–7 cps range; vertex sharp waves may occur and are distinguishable from background EEG activity, maximal over the central region; slow eye movements typically are present; rapid eye movements are absent; tonic electromyographic (EMG) levels are usually below those of relaxed wakefulness.
  - **Stage N2:** the presence of sleep spindles and/or K complexes (maximal over the central region) and the absence of sufficient high-amplitude, slow activity to define the presence of stage N3 sleep
  - **Stage N3:** an EEG (epoch) with ≥20% of an epoch consisting of slow, high amplitude waveforms of 0.5–2 Hz and peak-to-peak amplitude of >75mV.
  - **Stage R:** rapid eye movement (REM) sleep is defined by the concomitant appearance of LAMF EEG activity and episodic REMs; sawtooth waves (2–6 Hz waves maximal over the central region) may be present; chin EMG activity is typically low, and REM sleep is not scored in the presence of relatively elevated tonic mental-submental EMG activity.
  - **Awakening:** 2 consecutive epochs of Wake.
  - **Latency to onset of Persistent Sleep:** reported in minutes, defined as latency from Lights Off to the first epoch of 20 consecutive epochs of non-Wake.