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

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Poster

Supplemental materials

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DUET STUDY 407

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Introduction

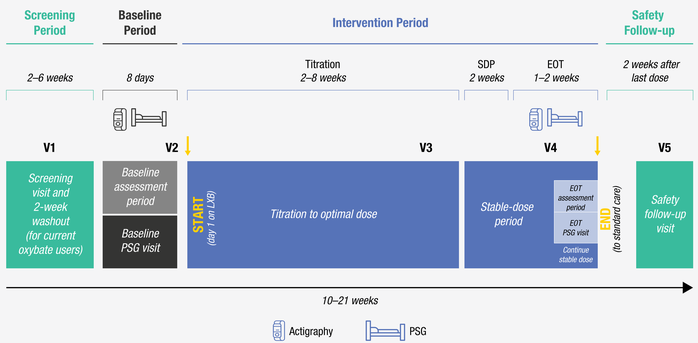
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat idiopathic hypersomnia in adults and excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) 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 idiopathic hypersomnia or narcolepsy (type 1 or type 2)
  - For results from the narcolepsy cohort of DUET, please refer to Poster 166

Objective

- To evaluate the effectiveness and safety of LXB on EDS and other idiopathic hypersomnia symptoms in participants with idiopathic hypersomnia

Methods

Figure 1. Study Design



EOT, end of treatment; LXB, low-sodium oxybate; 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
  - During DUET, participants with idiopathic hypersomnia could take once- or twice-nightly doses of LXB
- Participants were 18 to 75 years of age with a primary diagnosis of idiopathic hypersomnia meeting the *International Classification of Sleep Disorders – Third Edition* (ICSD-3) 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 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 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 on the bottom right corner of this poster
- Secondary endpoints for the idiopathic hypersomnia cohort included the Idiopathic Hypersomnia Severity Scale (IHSS) and Patient Global Impression of Change (PGIc) for overall idiopathic hypersomnia symptoms and for sleep inertia
- Safety endpoints included the 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 Idiopathic Hypersomnia

Characteristic	Safety Set[a] (N=46)
Age (years)	
Mean (SD)	38.1 (11.8)
Median (min, max)	37.5 (20.0, 68.0)
Sex at birth, n (%)	
Male	9 (19.6)
Female	37 (80.4)
Intersex	0
Declined to state	0
Gender identity, n (%)	
Male (including transgender man)	10 (21.7)
Female (including transgender woman)	36 (78.3)
Non-binary	0
Other	0
Declined to state	0
Participant of childbearing potential, n (%)	
Yes	27 (73.0)
Race, n (%)	
White	39 (84.8)
Black or African American	3 (6.5)
American Indian or Alaska Native	0
Asian	2 (4.3)
Native Hawaiian or other Pacific Islander	1 (2.2)
Multiple	1 (2.2)
Ethnicity, n (%)	
Hispanic or Latino	10 (21.7)
Not Hispanic or Latino	35 (76.1)
Body mass index (kg/m²)	
Mean (SD)	28.5 (6.4)
Median (min, max)	28.2 (17.1, 45.1)
Oxybate type at study entry, n (%)	
Naive[b]	37 (80.4)
Low-sodium oxybate	9 (19.6)
Sodium oxybate	0
Fixed-dose sodium oxybate	0

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

- Forty-six participants with idiopathic hypersomnia enrolled in the study and took ≥1 dose of study drug after the baseline period; most were female (80.4%) and White (84.8%)

Table 2. Mean LXB Dose and Regimen During the Stable-Dose Period

Mean (SD), grams	Safety Set[a] (N=41)
Once-nightly LXB dose (n=15)	4.8 (1.1)
Total twice-nightly LXB dose (n=26)	7.7 (1.2)
First nightly LXB dose	4.0 (0.8)
Second nightly LXB dose	3.6 (0.8)

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

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

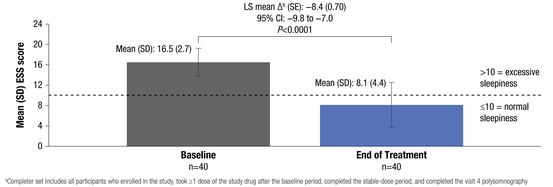
Table 3. Concomitant Alerting Medications

ATC Level 4 Term, n (%) Preferred term, n (%)	Safety Set[a] (N=46)
Participants taking a concomitant alerting agent[b], n (%)	19 (41.3)
Centrally acting antiobesity products	2 (4.3)
Benzphetamine	1 (2.2)
Phentermine	1 (2.2)
Centrally acting sympathomimetics	16 (34.8)
Amphetamine aspartate; amphetamine sulfate; dexamphetamine saccharate; dexamphetamine sulfate	8 (17.4)
Solriamfetol hydrochloride	5 (10.9)
Dexamphetamine sulfate	2 (4.3)
Methylphenidate	2 (4.3)
Modafinil	2 (4.3)
Dexamphetamine	1 (2.2)
Other antidepressants	6 (13.0)
Bupropion hydrochloride	6 (13.0)
Other nervous system drugs	1 (2.2)
Pitolisant hydrochloride	1 (2.2)

[a]Safety set includes all participants who enrolled in the study and took ≥1 dose of the study drug after the baseline period.
[b]It is not known whether these agents were prescribed for excessive sleepiness, idiopathic hypersomnia, or another condition.
[c]Concomitant medications had a stop date on or after date of first dose of study intervention or were ongoing.
ATC, anatomic therapeutic chemical.

- Nineteen participants (41%) took concomitant alerting agents

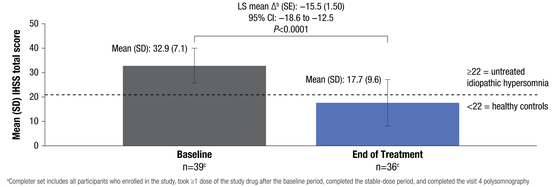
Figure 2. Epworth Sleepiness Scale Score[a]



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

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

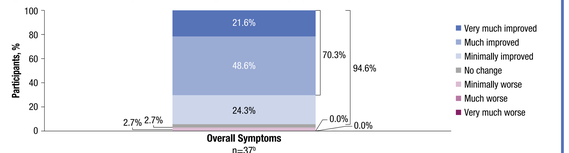
Figure 3. Idiopathic Hypersomnia Severity Scale Scores[a]



[a]Completer set includes all participants who enrolled in the study, took ≥1 dose of the study drug after the baseline period, completed the stable-dose period, and completed the visit 4 polysomnography end-of-treatment visit.
[b]Difference between end of treatment and baseline.
[c]Not all participants completed all assessments.
CI, confidence interval; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least-squares; SD, standard deviation; SE, standard error.

- Participants with idiopathic hypersomnia taking LXB showed improvements in idiopathic hypersomnia symptom severity on the IHSS from baseline to end of treatment

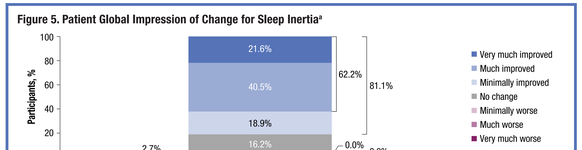
Figure 4. Patient Global Impression of Change for Overall Symptoms[a]



[a]Completer set includes all participants who enrolled in the study, took ≥1 dose of the study drug after the baseline period, completed the stable-dose period, and completed the visit 4 polysomnography end-of-treatment visit.
[b]Not all participants completed all assessments.

- Most participants reported improvement (very much, much, or minimal) on the PGIc for overall symptoms (94.6%)
  - Most participants reported improvement (very much or much) on the PGIc for overall symptoms (70.3%)

Figure 5. Patient Global Impression of Change for Sleep Inertia[a]



[a]Completer set includes all participants who enrolled in the study, took ≥1 dose of the study drug after the baseline period, completed the stable-dose period, and completed the visit 4 polysomnography end-of-treatment visit.
[b]Not all participants completed all assessments.

- Most participants reported improvement (very much, much, or minimal) on the PGIc for sleep inertia (81.1%)
  - A majority of participants reported improvement (very much or much) on the PGIc for sleep inertia (62.2%)

Table 4. Treatment-Emergent Adverse Events

Participants, n (%)	Safety Set[a] (N=46)
With ≥1 TEAE	34 (73.9)
With ≥1 TEAE related to treatment	30 (65.2)
With ≥1 serious TEAE	1 (2.2)
With ≥1 serious TEAE related to treatment	0
With ≥1 TEAE leading to discontinuation	1 (2.2)
TEAEs occurring in ≥5% of participants	
Nausea	9 (19.6)
Dizziness	8 (17.4)
Headache	8 (17.4)
Vomiting	5 (10.9)
Middle insomnia	4 (8.7)
Anxiety	3 (6.5)
Decreased appetite	3 (6.5)
Enuresis	3 (6.5)
Somnolence	3 (6.5)

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

- Thirty-four participants (73.9%) reported a TEAE
- One participant discontinued treatment due to a TEAE (depression)
- There was 1 serious adverse event of 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

- This study provides prospective data on LXB treatment of idiopathic hypersomnia and offers insights into common idiopathic hypersomnia symptoms in a real-world clinical setting
- Participants with idiopathic hypersomnia taking open-label, individually optimized LXB demonstrated improvements in EDS, sleep inertia, and idiopathic hypersomnia symptoms
  - The study is limited by its open-label design and the lack of a control cohort, which limits the ability to attribute the findings to LXB
- Overall, TEAEs were consistent with the known safety profile of LXB
- These results reinforce the burden of symptoms experienced by people living with idiopathic hypersomnia, and further support LXB as an effective treatment for idiopathic hypersomnia

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.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **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 in accordance with the statistical analysis plan using the Completer Set for the following endpoints for the idiopathic hypersomnia cohort:
  1. Epworth Sleepiness Scale (ESS) total score (decrease from baseline)
  2. Idiopathic Hypersomnia Severity Scale (IHSS) total score (decrease from baseline)
- Decreases from baseline for ESS and IHSS total scores 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 in which ESS endpoints were tested first, followed by IHSS endpoints. 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.