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Effectiveness and Safety of Low-Sodium Oxybate in Idiopathic Hypersomnia Participants: Results From the DUET Study

DUET STUDY 407

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Introduction

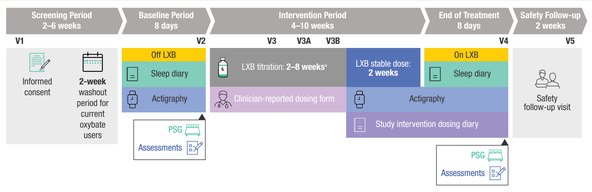
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration to treat idiopathic hypersomnia in adults and excessive daytime sleepiness (EDS) or cataplexy in patients ≥7 years of age with narcolepsy[1-4]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, multicenter, single-arm, multiple-cohort, open-label study (NCT05875974)
- This patient-centric study evaluated the effectiveness of LXB on nighttime and daytime symptoms and functional outcomes in participants with idiopathic hypersomnia or narcolepsy (type 1 or type 2)
  - For results from the narcolepsy cohort, please refer to Poster 393

Objective

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

Methods

Figure 1. Study Design



[a]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), as needed. Investigator could optimize participant dosage and move participant to stable dose 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 (with a 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 were taking their optimized stable dose of LXB (ending with an overnight EOT PSG with additional assessments), and a 2-week safety follow-up
  - Participants with idiopathic hypersomnia had the option of a once- or twice-nightly LXB dosing regimen (per the US prescribing information)[1]
- Eligible participants were adults 18 to 75 years of age with a primary diagnosis of idiopathic hypersomnia (meeting the *International Classification of Sleep Disorders – Third Edition*[5] [ICSD-3] criteria)
- Participants were required to have an Epworth Sleepiness Scale (ESS) score >10 at screening visit 1 or an ESS score >10 after the washout period, if currently taking an oxybate medication
- Participants were allowed to continue taking concomitant 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 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*),[6] as assessed during the BL PSG visit
  - History/presence of an unstable or clinically significant medical condition or 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 the conduct of the study, as determined by the investigator
- The primary endpoint was change in ESS score from BL to EOT
- The key secondary endpoint for the idiopathic hypersomnia cohort was change in Idiopathic Hypersomnia Severity Scale (IHSS) total score from BL to EOT
- Additional secondary endpoints included the Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C), both assessing overall idiopathic hypersomnia disease and sleep inertia
- Exploratory endpoints included the IHSS component scores for daytime functioning (composed of items 5, 9, 10, 11, 12, 13, and 14) and long sleep duration/sleep inertia (composed of items 1, 2, 3, 4, and 8)[7]
- 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 cohort: N=46); 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 (taking a dosage of up to 9 g/night), and completed the PSG EOT visit (idiopathic hypersomnia cohort: n=40)
- Details on statistical methodology are available through the QR code on the bottom right corner of this poster

Results

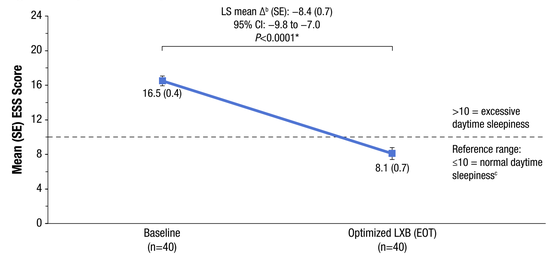
Table 1. Demographics and Baseline Characteristics for Enrolled Participants With Idiopathic Hypersomnia[a]

Characteristic	Idiopathic Hypersomnia Cohort (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)
Gender identity, n (%)	
Male (including transgender man)	10 (21.7)
Female (including transgender woman)	36 (78.3)
Nonbinary	0
Other	0
Declined to state	0
Participant of childbearing potential, n (%)	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[b]	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,[c] n (%)	
Naive[d]	37 (80.4)
Low-sodium oxybate	9 (19.6)
Sodium oxybate	0
Once-nightly sodium oxybate	0
Oxybate total nightly dosage at screening[e] (g)	
Mean (SD)	6.8 (2.2)
Median (min, max)	6.8 (3.8, 9.0)

[a]Safety analysis set. [b]Participant reported >1 race. [c]Nine participants 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 who were taking an oxybate at screening and prior to washout.
max, maximum; min, minimum; SD, standard deviation.

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

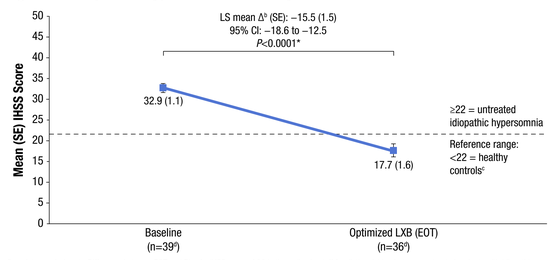
Figure 2. Epworth Sleepiness Scale Score[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]Established categories consider scores up to 10 normal.[8] The MCID for ESS was defined as 2 points according to an AASM systematic review and meta-analysis.[9] An ESS score >10 at screening was required for inclusion in DUET. *Controlled for multiplicity.
AASM, American Academy of Sleep Medicine; BL, baseline; CI, confidence interval; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LS, least squares; LXB, low-sodium oxybate; MCID, minimal clinically important difference; SE, standard error.

- Participants with idiopathic hypersomnia taking LXB showed a statistically significant reduction in ESS score from BL to EOT (mean [SE], -8.4 [0.7])

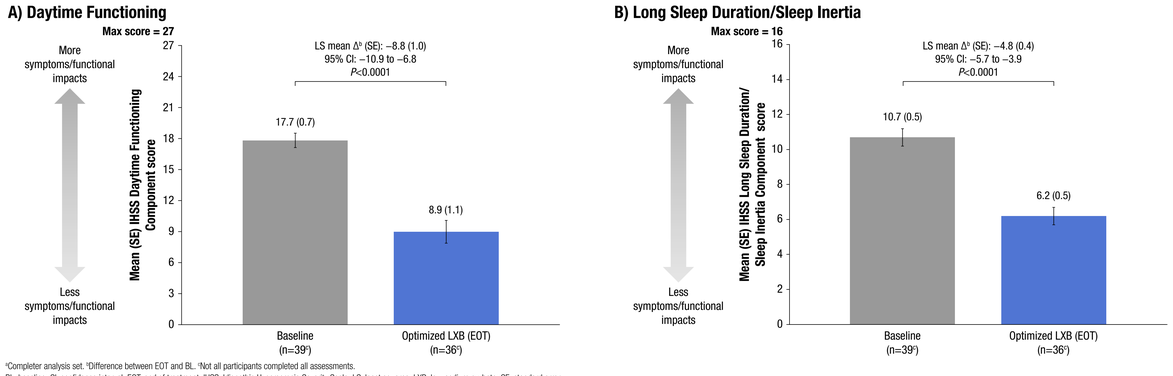
Figure 3. Idiopathic Hypersomnia Severity Scale Scores[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]An IHSS score of 22 is the optimal cutoff for distinguishing between untreated patients with idiopathic hypersomnia and community-dwelling controls.[10] [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; SE, standard error.

- Participants with idiopathic hypersomnia taking LXB showed a statistically significant reduction in the IHSS total score from BL to EOT (mean [SE], -15.5 [1.5])

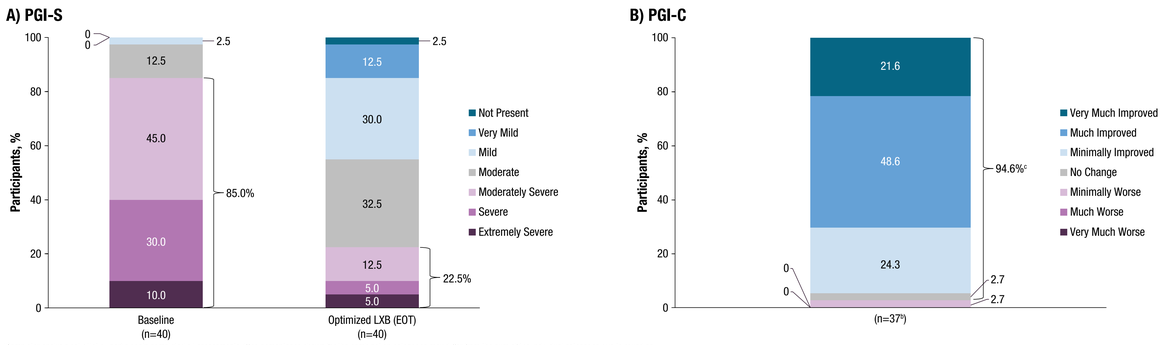
Figure 4. Idiopathic Hypersomnia Severity Scale Component Scores for Daytime Functioning (A) and Long Sleep Duration/Sleep Inertia (B)[a]



[a]Completer analysis set. [b]Difference between EOT and BL. [c]Not all participants completed all assessments.
BL, baseline; CI, confidence interval; EOT, end of treatment; IHSS, Idiopathic Hypersomnia Severity Scale; LS, least squares; LXB, low-sodium oxybate; SE, standard error.

- Participants with idiopathic hypersomnia taking LXB showed improvements in daytime functioning and long sleep duration/sleep inertia on the IHSS component scores from BL to EOT

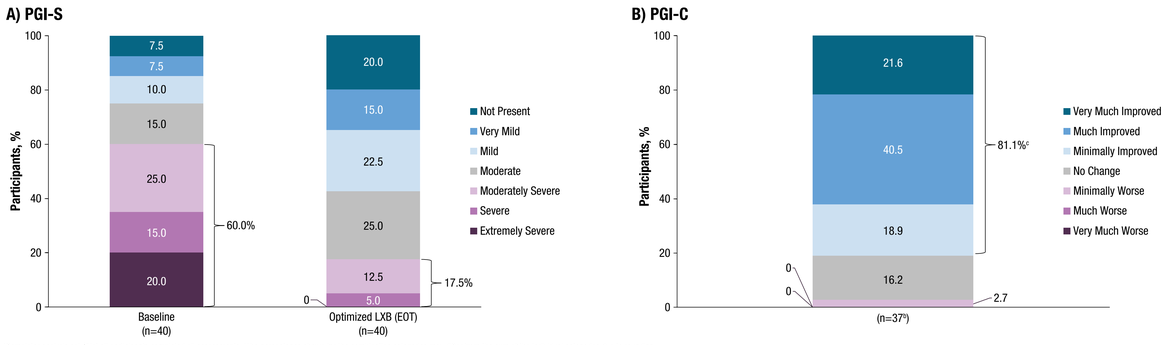
Figure 5. Patient Global Impression of Severity (A) and Patient Global Impression of Change (B) for Overall Idiopathic Hypersomnia Disease[a]



[a]Completer analysis set. [b]Not all participants completed all assessments. [c]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
EOT, end of treatment; LXB, low-sodium oxybate; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

- On the PGI-S, at BL, 85.0% of participants reported their overall idiopathic hypersomnia disease as moderately severe, severe, or extremely severe, compared with 22.5% ($P<0.0001$) at EOT
  - At EOT, 45.0% of participants reported their overall idiopathic hypersomnia disease as being not present, very mild, or mild
- On the PGI-C, at EOT, 94.6% (95% CI: 81.8–99.3) of participants reported improvement (very much, much, or minimal) for overall idiopathic hypersomnia disease

Figure 6. Patient Global Impression of Severity (A) and Patient Global Impression of Change (B) for Sleep Inertia[a]



[a]Completer analysis set. [b]Not all participants completed all assessments. [c]The percentages shown for the combination categories may differ from the sum of the individual categories due to rounding.
PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

- On the PGI-S, at BL, 60.0% of participants reported their sleep inertia severity as moderately severe, severe, or extremely severe, compared with 17.5% ($P=0.0002$) at EOT
  - At EOT, 57.5% of participants reported their sleep inertia as being not present, very mild, or mild
- On the PGI-C, at EOT, 81.1% (95% CI: 64.8–92.0) of participants reported improvement (very much, much, or minimal) for sleep inertia

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

Mean (SD), grams	Idiopathic Hypersomnia Cohort (N=41[a])
Once-nightly LXB (n=15)	
Mean (SD)	4.8 (1.1)
Twice-nightly LXB (n=26)	
Mean (SD)	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 analysis set who reached the SDP. Once a participant reached an optimized dosage, they continued this dosage as a stable regimen during the SDP and EOT period.
EOT, end of treatment; LXB, low-sodium oxybate; SD, standard deviation; SDP, stable-dose period.

- Fifteen participants (36.6%) were taking LXB once nightly and 26 participants (63.4%) were taking LXB twice nightly

Table 3. Concomitant Alerting Medication for Enrolled Participants With Idiopathic Hypersomnia[a]

Preferred Term, n (%)	Idiopathic Hypersomnia Cohort (N=46)
Participants taking a concomitant alerting agent,[b,c,d] n (%)	19 (41.3)
Centrally acting antiobesity products	
Benzphetamine	1 (2.2)
Phentermine	1 (2.2)
Centrally acting sympathomimetics	
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	
Bupropion hydrochloride	6 (13.0)
Other nervous system drugs	
Pitolisant hydrochloride	1 (2.2)

[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, idiopathic hypersomnia, and/or another condition. [d]Concomitant medications were started prior to the first dose of LXB and were ongoing throughout the study or could have been stopped after the first dose of LXB.
LXB, low-sodium oxybate.

- At study entry, 19 participants (41.3%) were taking alerting agents, with amphetamines being the most common (17.4%)

Table 4. Treatment-Emergent Adverse Events[a]

Participants, n (%)	Idiopathic Hypersomnia Cohort (N=46)
With ≥1 TEAE	34 (73.9)
With ≥1 TEAE related to treatment	30 (65.2)
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 analysis set.
TEAE, treatment-emergent adverse event.

- The overall TEAE rate was 73.9% in the idiopathic hypersomnia cohort
  - One serious TEAE of hypoxia (concurrent with influenza) was reported; it was moderate in severity, determined to be unrelated to the study drug according to the investigator, and resolved
- TEAEs were mild or moderate in severity; 1 participant with idiopathic hypersomnia discontinued treatment due to a TEAE of depression

Conclusions

- Participants with idiopathic hypersomnia taking open-label LXB showed improvements in EDS and nighttime and daytime symptoms (reduced ESS and IHSS component scores) and reported reduced symptom burden (decreased IHSS total scores and improved PGI-S and PGI-C ratings)
- This study provides prospective data on LXB treatment of idiopathic hypersomnia
  - Limitations of the study include the open-label and single-arm design; causality cannot be established
  - Analyses were based on the completer analysis set of participants who reached a stable LXB dosage and may not represent the experience of all individuals starting LXB treatment
- TEAEs were consistent with the known safety profile of LXB
- These findings highlight the significant symptom burden experienced by individuals with idiopathic hypersomnia, and reinforce the established effectiveness of LXB as a treatment for this condition

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.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition.* Darien, IL: American Academy of Sleep Medicine; 2014. **6.** 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. **7.** Rassu AL, et al. *J Clin Sleep Med.* 2022;18(2):617-629. **8.** Johns MW. *Sleep.* 1991;14(6):540-545. **9.** Maski K, et al. *J Clin Sleep Med.* 2021;17(9):1895-1945. **10.** Dauvilliers Y, et al. *Neurology.* 2019;92(15):e1754-e1762.

Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Under the direction of the authors, Peloton Advantage, LLC (an OPEN Health company), employees Duprane Young, PhD, Emily Bruggeman, PhD, and Karyn Liu, PhD, provided medical writing support and Katie Herman provided editorial support for this poster, which were funded by Jazz Pharmaceuticals.

Disclosures: DT Plante is a consultant and advisory board member for Jazz Pharmaceuticals. He has also served as a consultant/advisory board member for Alkermes, Harmony Biosciences, Centessa, and Takeda and a consultant for Aditum Bio, LLC, and Teva Pharmaceuticals (Australia). **A Cairns** is a consultant and advisory board member for Jazz Pharmaceuticals and, during the course of this project, was an employee of BioSerenity and received grant funding from Jazz Pharmaceuticals. **LD Schneider** has received personal compensation for serving on advisory boards and speakers bureaus for Jazz Pharmaceuticals, Eisai, and Avadel. **DA Nichols, DS Fuller, MT Kirby, S Akerman, JK Alexander,** and **M Whalen** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **TL Steininger** is a former full-time employee and current contract worker for Jazz Pharmaceuticals who has received shares of Jazz Pharmaceuticals, plc. **CM Ruoff** has served as an advisory board member for Jazz Pharmaceuticals, Eisai, Alkermes, and Takeda, and has received grant funding from Jazz Pharmaceuticals.

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Presented at SLEEP 2025, the 39th Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS); June 8–11, 2025; Seattle, WA, USA

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Supplemental Statistical Methods

- Formal hypothesis testing was conducted in accordance with the statistical analysis plan using the completer analysis set for the following endpoints:
  1. Epworth Sleepiness Scale (ESS) score (decrease from baseline [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 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 in which the ESS endpoint was tested first, followed by the IHSS endpoint. The Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), and IHSS component scores were not controlled for multiplicity. 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. *P* values for comparisons of proportions of participants at BL versus EOT reporting “moderately severe/severe/extremely severe” on the PGI-S assessments were obtained from the McNemar test. Exact 95% CIs were obtained using the Clopper-Pearson method for the proportion of participants rating “minimal/much/very much” improvement at EOT on the PGI-C assessments.