092

Reduction in Sleep Inertia and Components of Daytime Sleepiness in Idiopathic Hypersomnia With Low-Sodium Oxybate Treatment in the Phase 4 DUET Study

DUET STUDY 407

Hans P. A. Van Dongen, PhD[1]; Logan D. Schneider, MD[2]; Chad M. Ruoff, MD[3]; Jing Dai, PhD[4]; Deborah A. Nichols, MS[4]; Teresa L. Steininger, PhD[4]; M. Todd Kirby, PhD[5,6]; Marisa Whalen, PharmD[5]; Alyssa Cairns, PhD[5]; David T. Plante, MD, PhD[7]

[1]Sleep and Performance Research Center, Washington State University Health Sciences Spokane, Spokane, WA, USA; [2]Stanford University Center for Sleep Sciences and Medicine, Palo Alto, CA, USA; [3]Center for Sleep Medicine, Mayo Clinic, Scottsdale, AZ, USA; [4]Jazz Pharmaceuticals, Palo Alto, CA, USA; [5]Jazz Pharmaceuticals, Philadelphia, PA, USA; [6]Department of Psychiatry & Health Behavior, Medical College of Georgia at Augusta University, Augusta, GA, USA; [7]Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

Introduction

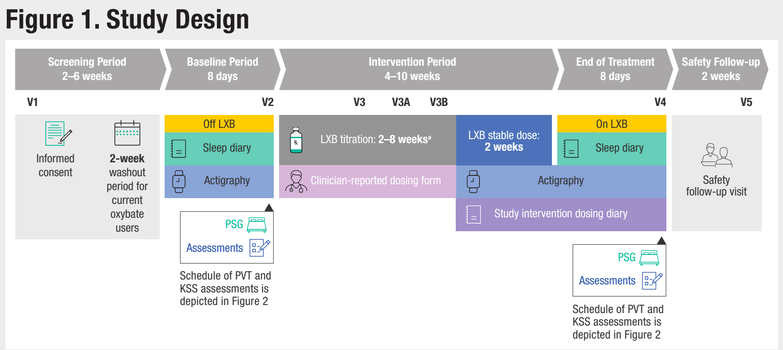
- Sleep inertia is a common symptom of idiopathic hypersomnia, characterised as prolonged difficulty awakening with repeated returns to sleep, irritability, and/or confusion.[1] Sleep inertia is also reported in narcolepsy, but is reported more frequently and/or severely in idiopathic hypersomnia[2-5]
- Low-sodium oxybate (LXB; Xywav®) is approved in the United States to treat idiopathic hypersomnia in adults and excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy[6-9]
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment) was a phase 4, prospective, open-label study (NCT05875974) to assess the effectiveness of LXB treatment on sleep and daytime symptoms in patients with idiopathic hypersomnia or narcolepsy

Objective

- The aim of the present analysis was to estimate the magnitude and temporal dynamics of sleep inertia and sleepiness during the first 2 hours after awakening in participants with idiopathic hypersomnia treated with LXB

Methods

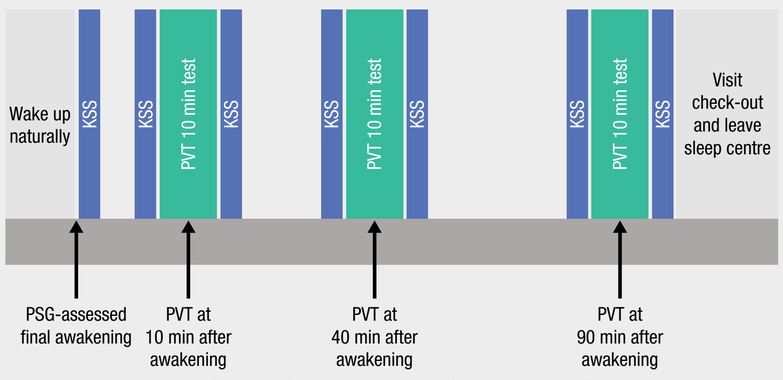
Figure 1. Study Design



Adapted from Nichols DA, et al. *Neurol Ther.* 2025;14:1705–727. http://creativecommons.org/licenses/by-nc/4.0/.
[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 optimise 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 current oxybate users), a baseline (BL) period, a titration period (participants began LXB treatment with individualised dosing adjustments to achieve their optimal dose), a stable-dose period (SDP; at the optimal LXB dose), an end-of-treatment (EOT) period, and a safety follow-up
  - Participants could be treated with a once- or twice-nightly LXB dosing regimen based on the investigator's discretion in the idiopathic hypersomnia cohort (per US prescribing label)[6]
- At BL and EOT, participants underwent nocturnal polysomnography (PSG) and assessments were administered

Figure 2. Schedule of PVT and KSS Assessments on the Morning After PSG at BL and EOT



BL, baseline; EOT, end of treatment; KSS, Karolinska Sleepiness Scale; min, minute; PSG, polysomnography; PVT, Psychomotor Vigilance Test.

- Exploratory endpoints included the Psychomotor Vigilance Test (PVT; an objective measure of alertness impairment) and the Karolinska Sleepiness Scale (KSS; a subjective measure of sleepiness at a specific moment)
  - The PVT and KSS were administered multiple times after awakening following the PSG on Visit 2 (pre-treatment; BL) and Visit 4 (optimised LXB; EOT) to measure sleep inertia
- The 10-minute PVT, a reaction-time task requiring participants to respond as quickly and accurately as possible to a visual stimulus,[10] was completed 10, 40, and 90 minutes after the PSG-assessed final awakening
  - Evaluates the ability to sustain attention and measures objective alertness impairment and sleep inertia (based on its temporal relation to awakening)
  - The key outcome was lapses of attention (reaction times >500 ms)
- The KSS, a single-item, self-report scale, was completed within 2 minutes after the PSG-assessed final awakening and immediately before and after each PVT assessment
  - Measures situational sleepiness in the last 10 minutes using a 9-point scale (1="extremely alert" to 9="very sleepy, great effort to keep awake, fighting sleep")[11]
- Nonlinear, mixed-effects regression models on PVT lapses (reaction times >500 ms) and KSS ratings at the assessed time points were used to estimate objective alertness impairment and subjective sleepiness, respectively, at awakening and 2 hours after awakening. The models estimated the magnitude of sleep inertia (the portion of objective alertness impairment or subjective sleepiness that dissipates after awakening)
  - The model accounted for systematic inter-individual differences and heteroskedastic error variance; *P* values are nominal

Figure 3. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- 18–75 years of age with primary diagnosis of idiopathic hypersomnia (per ICSD-3 criteria)
  - Individuals with and without long sleep time were included[a]
- ESS score >10[b]
- 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

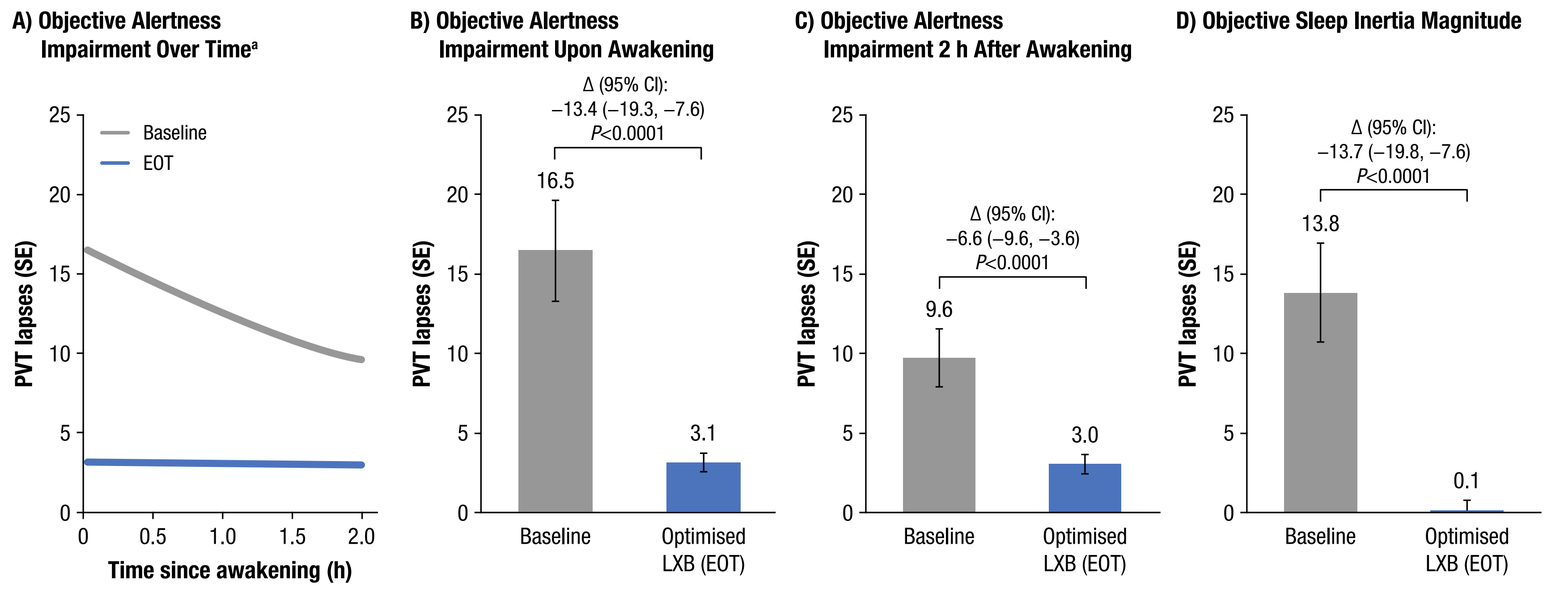
Key Exclusion Criteria

- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[c]
- History/presence of other untreated/inadequately treated sleep disorder or unstable/clinically significant medical condition, behavioural/psychiatric disorder, neurologic disorder, or surgical history that might affect the participant's safety or interfere with study conduct

[a]Analyses are performed for the complete idiopathic hypersomnia cohort, with no distinction made between those with and without long sleep time. [b]At screening visit 1 or at visit 2 if currently taking an oxybate medication, after the washout period. [c]Hypopnoea definition included ≥4% desaturation per Rule 1B of *The AASM Manual for the Scoring of Sleep and Associated Events*,[12] as assessed during the baseline PSG visit.
AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; ICSD-3, *International Classification of Sleep Disorders – Third Edition*; PSG, polysomnography.

Results

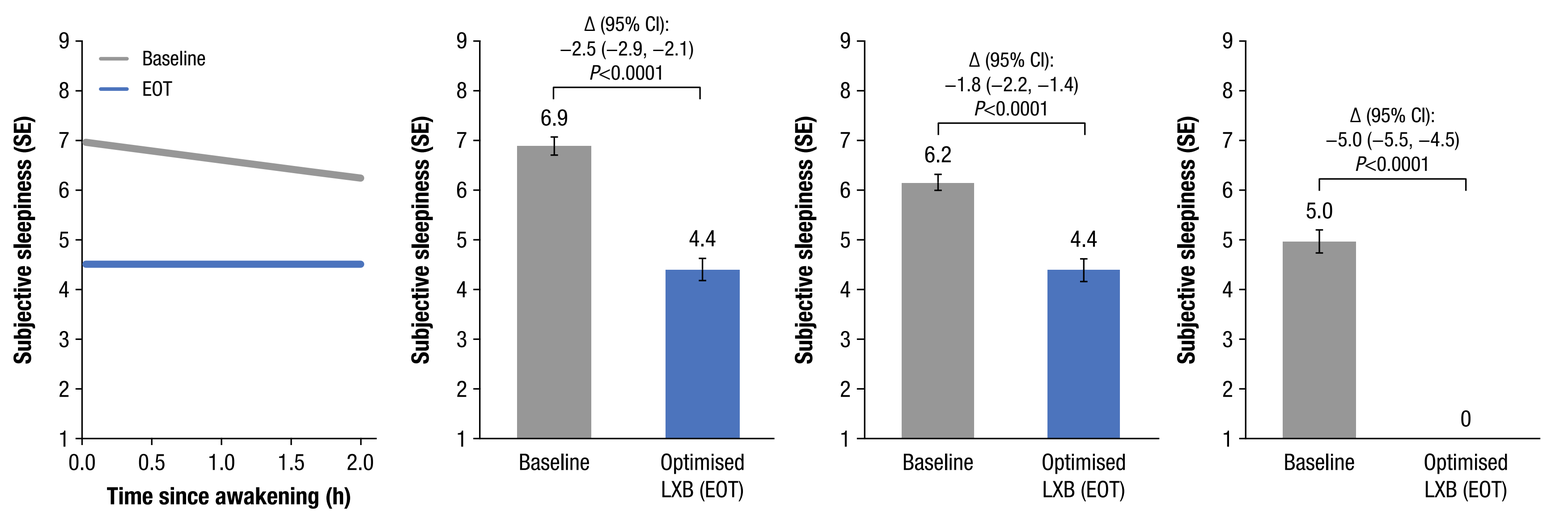
Figure 4. PVT Results for Objective Alertness Impairment and Sleep Inertia



[a]The sleep inertia dissipation time constant, a standard measure of exponential decay that indicates how long it takes for sleep inertia to reduce by 63.2%, was 2.9 hours (SE: 1.2 hours; 95% CI: 0.5, 5.3 hours).
CI, confidence interval; h, hours; EOT, end of treatment; LXB, low-sodium oxybate; PVT, Psychomotor Vigilance Test; SE, standard error.

- Based on PVT modeling results (n=40), objective alertness impairment was reduced and sleep inertia magnitude decreased substantially with optimised LXB treatment

Figure 5. KSS Results for Subjective Sleepiness and Sleep Inertia



[a]The sleep inertia dissipation time constant, a standard measure of exponential decay that indicates how long it takes for sleep inertia to reduce by 63.2%, was 12.4 hours (SE: 3.9 hours; 95% CI: 4.6, 20.3 hours).
CI, confidence interval; EOT, end of treatment; h, hours; KSS, Karolinska Severity Scale; LXB, low-sodium oxybate; SE, standard error.

- Based on KSS modeling results (n=40), subjective sleepiness was reduced and sleep inertia magnitude decreased substantially with optimised LXB treatment

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)
Sex at birth, n (%)	
Male	9 (19.6)
Female	37 (80.4)
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)
Body mass index (kg/m²), mean (SD)	28.5 (6.4)
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)
Concomitant alerting agents, n (%)	19 (41.3)

[a]Safety analysis set, which includes all participants who enrolled in the study and took their prescribed LXB regimen for ≥1 night after the BL period. [b]Participant reported >1 race. [c]Screening period included a 2-week washout for current oxybate users. [d]No oxybate use within 2 weeks of entering the study. [e]For the participants who were taking an oxybate at screening.
BL, baseline; max, maximum; min, minimum; SD, standard deviation.

- Forty-six people with idiopathic hypersomnia enrolled and took LXB for ≥1 night; 40 completed the study
  - Nine (19.6%) participants were taking oxybate at study entry prior to washout
- Most enrolled participants were female (80.4%) and White (84.8%); the mean (SD) age was 38.1 (11.8) years

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

	Idiopathic Hypersomnia Cohort (n=41[a])
Total once-nightly LXB dosage (g/night)	n=15
Mean (SD)	4.8 (1.1)
Total twice-nightly LXB dosage (g/night)	n=26
Mean (SD)	7.7 (1.2)
First nightly LXB dose, mean (SD)	4.0 (0.8)
Second nightly LXB dose, mean (SD)	3.6 (0.8)

[a]Includes participants from the safety analysis set who reached the SDP. Once a participant reached an optimised 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 (36.6%) participants were taking once-nightly LXB and 26 (63.4%) participants were taking twice-nightly LXB

Table 3. 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)
TEAEs occurring in ≥10% of participants	
Nausea	9 (19.6)
Dizziness	8 (17.4)
Headache	8 (17.4)
Vomiting	5 (10.9)

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

- TEAEs were mild or moderate in severity
- There was 1 serious TEAE (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

- Compared with baseline (off-LXB), participants with idiopathic hypersomnia on optimised LXB treatment demonstrated substantially reduced sleep inertia magnitude by subjective and objective measures, subjective reduction in sleepiness upon awakening, and objective improvement in impaired alertness
- TEAEs were consistent with the known LXB safety profile

References: 1. American Academy of Sleep Medicine. International Classification of Sleep Disorders – Third Edition. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** Bassetti C, et al. *Sleep Med.* 2003;4:7-12. **3.** Sung ER, et al. *Sleep Med.* 2024;121:352-8. **4.** Barateau L, et al. *Sleep.* 2024;47:zsad323. **5.** Vernet C, Arnulf I. *Sleep.* 2009;32:1229-35. **6.** Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **7.** Szarfman A, et al. *N Engl J Med.* 1995;333:1291. **8.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **9.** 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. **10.** Dinges DF, Powell JW. *Behav Res Methods Instrum Comput.* 1985;17:652-5. **11.** Shahid A, et al. S*TOP, THAT and One Hundred Other Sleep Scales.* New York, NY: Springer New York; 2012:209-10.
12. 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.

Support and Acknowledgements: This study was sponsored by Jazz Pharmaceuticals. Under the direction of the authors, Peloton Advantage, LLC (an OPEN Health company) employees Karyn Liu, PhD, and Emily Bruggeman, PhD, provided medical writing support and an editor provided editorial support, which were funded by Jazz Pharmaceuticals.

Disclosures: HPA Van Dongen serves as a consultant to Jazz Pharmaceuticals plc. **LD Schneider** is a compensated member of advisory boards and speakers bureaus for Eisai, Harmony Biosciences, and Jazz Pharmaceuticals. **CM Ruoff** has served as an advisory board member for Alkermes, Eisai, Jazz Pharmaceuticals, and Takeda, and has received grant funding from Jazz Pharmaceuticals. **J Dai, DA Nichols, MT Kirby,** 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. **A. Cairns** is a full-time contract employee and advisory board member for Jazz Pharmaceuticals. **DT Plante** is a consultant and advisory board member for Jazz Pharmaceuticals. He has also served as a consultant/advisory board member for Alkermes, Apnimed, Centessa, Harmony Biosciences, and Takeda, and a consultant for Aditum Bio and Teva Pharmaceuticals (Australia).

Scan this code to access this poster online. This code is not for promotional purposes.

Presented at World Sleep Congress; September 5–10, 2025; Singapore