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DUET STUDY 407

Individualized Dosing of Low-Sodium Oxybate in Patients With Narcolepsy or Idiopathic Hypersomnia

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Objective

- To analyze the dosing combinations utilized and adverse reactions most challenging to manage during low-sodium oxybate (LXB) treatment optimization in participants in the DUET study

Conclusions

- Small incremental adjustments enabled by the liquid LXB formulation support individualized dosing, allowing clinicians to meet patient needs and optimize treatment across a range of total nightly doses, equal or unequal dose division, and once- or twice-nightly dosing
- In DUET, study clinicians adjusted participants' LXB dosage and regimen to optimize effectiveness and tolerability, reaching a stable, optimal dose within ~6 weeks on average for idiopathic hypersomnia and narcolepsy cohorts, and within ~9 weeks for the narcolepsy >9 g cohort

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Morse AM, et al. *Neurol Ther.* 2024;13(3):785-807. **3.** Schneider LD, et al. *Nat Sci Sleep.* 2023;15:663-675. **4.** Arnulf I, et al. *Sleep Med Rev.* 2023;69:101766. **5.** Roy A, et al. *Nat Sci Sleep.* 2023;15:767-778. **6.** Nichols DA, et al. *Neurol Ther.* 2025;14(4):1705-1727. **7.** Plante DT, et al. *CNS Drugs.* 2026;Mar 14 Online Ahead of Print. **8.** Schneider LD, et al. *Neurol Ther.* 2026;April 30 Online Ahead of Print.

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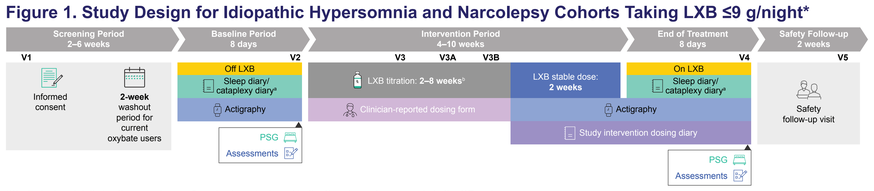
Introduction

- Low-sodium oxybate (LXB; Xywav®) is approved in the US for the treatment of cataplexy or excessive daytime sleepiness in patients ≥7 years of age with narcolepsy and for the treatment of idiopathic hypersomnia in adults[1]
- LXB is an oral solution administered twice nightly (equally or unequally divided) for adults with narcolepsy and once or twice nightly for adults with idiopathic hypersomnia[1]
- Individualized dosing of LXB is important for optimizing treatment effectiveness and tolerability and for meeting patient lifestyle needs, as supported by consensus recommendations, expert opinion, and physician survey results[2-5]

Methods

Figure 1. Study Design for Idiopathic Hypersomnia and Narcolepsy Cohorts Taking LXB ≤9 g/night*



*Study design details for the narcolepsy >9g cohort can be found in the Supplement, accessed via the QR code.
Figure adapted from Nichols DA, et. al. *Neurol Ther.* 2025;14:1705-27.[7] http://creativecommons.org/licenses/by-nc/4.0/.
[a]Cataplexy diary in 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), as needed. Clinician could optimize participant dosage and move 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.

- This was an exploratory analysis of the phase 4, prospective, single-arm, open-label DUET study (NCT05875974), which evaluated LXB in 3 cohorts of participants: 1) idiopathic hypersomnia (optimized LXB ≤9 g/night), 2) narcolepsy (optimized LXB ≤9 g/night), and 3) narcolepsy >9 g (optimized >9 g/night)
  - Primary results for the idiopathic hypersomnia cohort[7] and the narcolepsy ≤9 g/night cohort[8] have been published
- During a 2- to 8-week LXB titration period, clinicians optimized dosing for each participant per direction in study dosing guidance documents developed based on expert consensus recommendations[2] and LXB prescribing information.[1] For participants in the narcolepsy >9 g cohort, LXB doses were titrated under careful in-clinic supervision and the clinical judgment of the clinician (for the study design of the narcolepsy cohort taking LXB >9 g/night and for LXB titration guidance, please see the Supplement accessed via the QR code)
  - Participants in the idiopathic hypersomnia cohort received once- or twice-nightly LXB
  - Participants in the narcolepsy and narcolepsy >9 g cohorts received twice-nightly LXB

Figure 2. Key Enrollment Eligibility Criteria

Inclusion Criteria
- Adults aged 18–75 years with a primary diagnosis of narcolepsy (ICSD-3 or DSM-5) or idiopathic hypersomnia (ICSD-3)[a]
- ESS score >10[b]
- Stable use of concomitant anticataplectics or alerting agents allowed[c]
- For >9 g narcolepsy cohort – on 9 g of LXB at screening, or titrated up to 9 g in the main study, with clinician assessment of potential benefit from LXB dosage >9 g

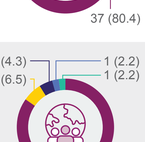
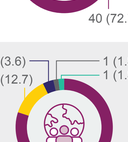
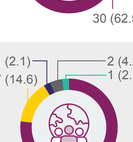
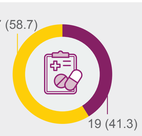
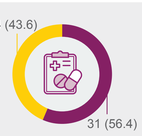
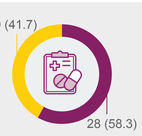
Exclusion Criteria
- Untreated/inadequately treated sleep-disordered breathing (AHI >10) at baseline PSG[d]
- History/presence of other untreated, inadequately treated, or unstable disorder or condition (eg, sleep, medical, behavioral/ psychiatric, neurologic)[e]
- Medication(s) contraindicated, with known drug-drug interaction, or similar EEG effects as LXB or known to have clinically significant CNS sedating effects

[a]Diagnosis of idiopathic hypersomnia and analyses performed for the idiopathic hypersomnia cohort make no distinction between those with and without long sleep time. [b]At screening visit 1 or, if taking an oxybate medication at screening, at visit 2; not applicable to the >9 g cohort. [c]Alerting agents were defined as stimulants or wake-promoting agents; participants must have taken the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study. [d]Hypopnea definition included a ≥4% desaturation as per Rule 1B of *The AASM Manual for the Scoring of Sleep and Associated Events*, as assessed during the baseline PSG visit. [e]As determined by the clinician.
AHI, apnea-hypopnea index; CNS, central nervous system; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; EEG, electroencephalogram; ESS, Epworth Sleepiness Scale; ICSD-3, *International Classification of Sleep Disorders – Third Edition*; LXB, low-sodium oxybate; PSG, polysomnography.

- Electronic clinician-reported dosing forms captured details of the treatment regimen weekly for each titration step and reasons for changes to better understand clinician dosage rationale and confirm the participant's optimized dosage
- Adverse reactions most challenging to manage were recorded at the end of the titration period, prior to the 2-week stable-dose period (SDP)
- Additional study methodology details can be found in the Supplement, accessed via the QR code

Results

Table 1. Demographics and Baseline Characteristics[a]

Characteristic	Idiopathic Hypersomnia (N=46)	Narcolepsy (N=55)[b]	Narcolepsy >9 g (N=48)
Age, years Mean (SD)	38.1 (11.8)	33.4 (12.9)	39.2 (10.9)
Oxybate type at study entry, n (%) Naive[c] Low-sodium oxybate Sodium oxybate Once-nightly sodium oxybate	37 (80.4) 9 (19.6) 0 0	42 (76.4) 6 (10.9) 5 (9.1) 2 (3.6)	0 48 (100) 0 0
Oxybate total nightly dosage at screening, g n Mean (SD) Median (min, max)	8 6.8 (2.2) 6.8 (3.8, 9.0)	11 7.4 (1.4) 7.0 (5.6, 9.0)	48 9 (0)[d] 9 (9.0, 9.0)[d]
Female at birth, n (%)	 37 (80.4)	 40 (72.7)	 30 (62.5)
Race, n (%) White Black or African American Asian Native Hawaiian or Other Pacific Islander Unknown Multiple	2 (4.3) 1 (2.2) 3 (6.5) 1 (2.2) 39 (84.8)	2 (3.6) 1 (1.8) 7 (12.7) 1 (1.8) 44 (80.0)	1 (2.1) 2 (4.2) 7 (14.6) 1 (2.1) 37 (77.1)
Body mass index, kg/m² Mean (SD)	 28.5 (6.4)	 29.5 (6.7)	 29.9 (8.9)
Concomitant alerting agent use, n (%)[e,f] Yes No	 27 (58.7) 19 (41.3)	 24 (43.6) 31 (56.4)	 20 (41.7) 28 (58.3)

[a]Safety analysis set. [b]Includes 13 participants who transferred to the narcolepsy >9 g cohort. [c]No oxybate use within 2 weeks before entering the study. [d]Part of entry criteria for >9 g narcolepsy cohort was to be on 9 g of LXB at screening, or titrated up to 9 g in the main study, with clinician assessment of potential benefit from LXB dosage >9 g. [e]Participants could have been taking multiple different alerting medications. [f]It is not known whether these agents were prescribed for excessive sleepiness, narcolepsy, and/or another condition.
LXB, low-sodium oxybate; max, maximum; min, minimum; SD, standard deviation.

Table 2. Most Challenging Adverse Reaction to Manage During Titration of LXB[a]

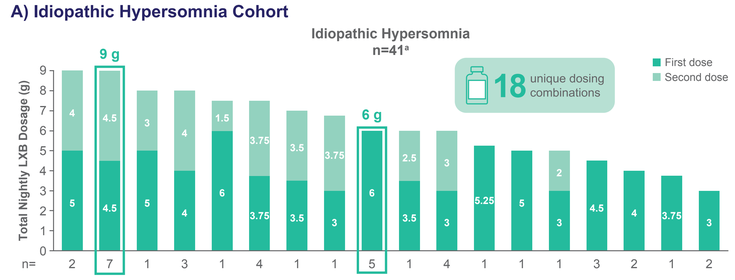
Adverse Reaction, %[b,c]	Idiopathic Hypersomnia (n=37)	Narcolepsy (n=31)	Narcolepsy >9 g (n=37)
None	48.6	41.9	67.6
Nausea (after first dose)	—	16.1	5.4
Nausea (upon awakening in AM)	5.4	6.5	—
Grogginess	2.7	6.5	—
Vomiting	2.7	6.5	2.7
Anxiety	5.4	3.2	2.7
Dizziness (between doses)	5.4	—	—
Morning confusion	—	—	5.4
	Lowest Highest	Lowest Highest	Lowest Highest

[a]Participants from the completer analysis set who completed the SDP, and for whom the clinician-reported dosing form was completed. [b]Percentage of clinicians endorsing that adverse reaction in their patients; clinicians were directed to choose 1 adverse reaction as the most challenging to manage. [c]Adverse reactions endorsed by >5% of clinicians are reported; dash indicates adverse reaction not reported.
AM, morning; LXB, low-sodium oxybate; SDP, stable-dose period.

- Most clinicians reported "none" for most challenging adverse reaction to manage (41.9%–67.6% across cohorts); 5.4% to 16.1% reported nausea (after first dose)
- TEAEs reported in ≥10% of participants during the entire study can be found in the Supplement, accessed via the QR code

Figure 3. Individualized Dosing Allowed for Use of Multiple Unique Dosage Combinations During the Stable-Dose Period

A) Idiopathic Hypersomnia Cohort



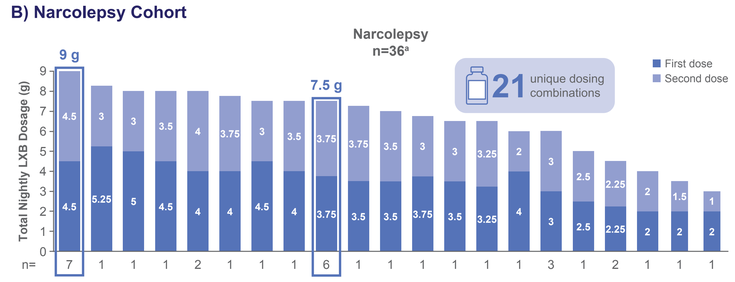
36.6% were once-nightly regimens (15/41 participants)

63.4% were twice-nightly regimens (26/41 participants)

Most common total nightly dosages: 9 g 17.1% (n=7; 2x nightly) 6 g 12.2% (n=5; 1x nightly)

Optimization Time (mean): 42.1 days (min: 14 days, max: 62 days)

B) Narcolepsy Cohort

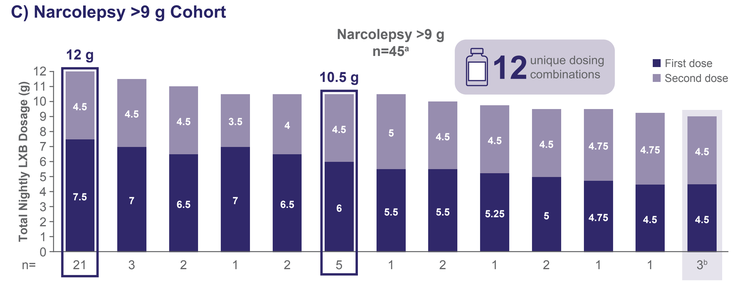


66.7% with equal doses (24/36 participants)

Most common total nightly dosages (all twice nightly): 9 g 19.4% (n=7) 7.5 g 16.7% (n=6)

Optimization Time (mean): 41.8 days (min: 12 days, max: 67 days)

C) Narcolepsy >9 g Cohort



97.6% with unequal doses (41/42 participants)

Most common total nightly dosages (all twice nightly): 12 g[c] 46.7% (n=21) 10.5 g 11.1% (n=5)

Optimization Time (mean): 63.4 days (min: 16 days, max: 142 days)

The most common dosages are indicated by boxes.
[a]Participants from the safety analysis set who completed the SDP. In the 3 cohorts, n=41 (idiopathic hypersomnia), n=36 (narcolepsy), and n=45 (narcolepsy >9 g), participants completed the SDP. [b]Only 42 of 45 participants were included in the number of unique doses in the >9 g cohort due to exclusion of 3 participants from the analysis who took 9 g (not >9g) during this period. [c]Maximum dosage allowed was 12 g.
LXB, low-sodium oxybate; SDP, stable-dose period.

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References: 1. Nichols DA, et al. *Neurol Ther.* 2025;14(4):1705-1727. **2.** Morse AM, et al. *Neurol Ther.* 2024;13(3):785-807.

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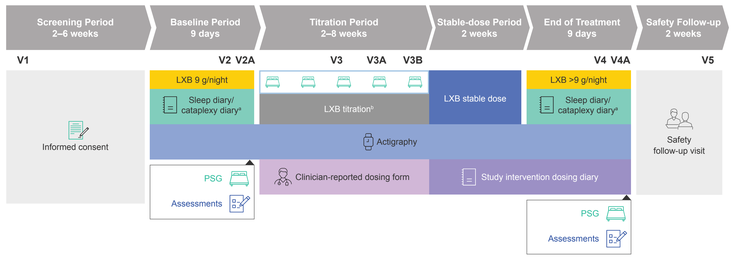
Supplemental Material

Supplemental Figure S1. Study Design for Narcolepsy >9 g Cohort



Adapted from Nichols DA, et al. *Neurol Ther.* 2025;14:1705–27.[1] http://creativecommons.org/licenses/by-nc/4.0/.
[a]Cataplexy diary in NT1 only. [b]Weekly titration visits with a dose escalation were performed as an overnight PSG visit for safety monitoring; visits without a dose escalation could be via teleconference. Titration could take between 2 and 8 weeks. V3 occurred on titration day 14. Additional in-clinic visits were scheduled for day 35 (V3A) and day 56 (V3B), as needed. Clinician could optimize participant dosage and move participant to SDP at V3, V3A, or V3B, but not during intervening weekly teleconferences.
LXB, low-sodium oxybate; NT1, narcolepsy type 1; PSG, polysomnography; SDP, stable-dose period; V, visit.

- Low-sodium oxybate (LXB) dosing
  - Idiopathic hypersomnia cohort: participants took a once- or twice-nightly LXB regimen based on the clinician's discretion (per US prescribing label; a maximum of 6 g/night for once-nightly or a maximum of 9 g/night for twice-nightly regimens, divided equally or unequally into 2 doses with the second dose taken 2.5–4 hours after the first dose)
  - Narcolepsy cohort: participants took LXB twice nightly (per US prescribing label; a maximum of 9 g/night for twice-nightly regimen, divided equally or unequally into 2 doses with the second dose taken 2.5–4 hours after the first dose)
  - Narcolepsy >9 g cohort: participants took LXB twice nightly (a maximum dose of 7.5 g for the first nightly dose and a second maximal dose of 4.5 g administered approximately 4 hours after the first dose)

Supplemental Figure S2. Dosage Titration for Participants With Idiopathic Hypersomnia or Narcolepsy Taking ≤9 g

Clinicians titrated LXB to an optimal dosage under the following requirements

- Oxybate naive: Initiate LXB at 4.5 g/night in 2 divided doses; for once-nightly dosing in idiopathic hypersomnia, initiate at 3 g/night
- Current oxybate: Initiate LXB at half of pre-washout dose and rapidly titrate back to previous dose (at clinician discretion)
- The recommended titration rate is increasing increments **up to 1.5 g per night per week**
- Dose increases may be made in 1 step per week, or may be made in 2 or more increments every few days as tolerated
- **For narcolepsy:** Maximum allowed total nightly dose is 9 g divided into 2 doses
- **For idiopathic hypersomnia:** Maximum allowed total nightly dose is 9 g divided into 2 doses; a single dose administration should not exceed 6 g/night
- Dose may be decreased **at any time** by any amount to address tolerability issues

LXB, low-sodium oxybate.

Supplemental Figure S3. Dosage Titration for Participants With Narcolepsy Taking >9g

Clinicians titrated LXB to an optimal dosage for participants in the >9 g cohort under the following requirements

- The first night for all LXB dose escalations above 9 g was conducted in the sleep laboratory clinic with PSG and appropriate in-clinic safety monitoring
- Each dose-escalation step during titration was limited to 0.5 g/night/week, up to a maximum of 12 g nightly
- All participants took twice-nightly LXB
  - The first nightly maximal dose was 7.5 g
  - The second nightly maximal dose was 4.5 g and was administered approximately 4 hours after the first dose

LXB, low-sodium oxybate; PSG, polysomnography.

Supplemental Table S1. Treatment-Emergent Adverse Events[a] (Occurring in ≥10% of Participants)

Participants, n (%)	Idiopathic Hypersomnia (N=46)	Narcolepsy (N=55)	Narcolepsy >9 g (N=48)
Nausea	9 (19.6)	13 (23.6)	6 (12.5)
Dizziness	8 (17.4)	8 (14.5)	—[b]
Headache	8 (17.4)	7 (12.7)	5 (10.4)
Vomiting	5 (10.9)	6 (10.9)	6 (12.5)
Somnolence	—[b]	6 (10.9)	—[b]

Lowest Highest Lowest Highest Lowest Highest

[a]Safety analysis set. [b]Reported by <10% of participants.

Supplemental Table S2. Summary of Titration Guidance Provided to Clinicians[a]

Concern	Dosing Adjustments to Consider
Guidance: Addressing Sleep Onset and Duration	
Difficulty falling asleep after first dose	• Review social, behavioral, food timing, environmental factors, and alignment of bedtime with natural sleep/wake rhythm • Increase the first dose
Difficulty falling asleep after second dose	• Increase second dose • Decrease duration between doses
Waking up very shortly after first dose (eg, <2 hours)	• Increase first dose • Allow for initial sleep period prior to administration of first dose
Waking too soon after second dose (eg, <2 hours)	• Delay second dose if waking is <4 hours after first dose • Increase second dose • Increase first dose and delay second dose
Unable to awaken for second dose	• Ensure 4 hours between doses (eg, no alarm earlier than 4 hours post-first dose) • Decrease first dose • For idiopathic hypersomnia: consider once-nightly regimen
Difficulty awakening at morning wake time	• If related to long sleep in idiopathic hypersomnia, titrate to a higher dose and/or take second dose earlier • If related to LXB (in either indication) decrease second dose and/or take second dose earlier
Guidance in Addressing Adverse Reactions/Tolerability	
Adverse Reaction	**Dosing Adjustments to Consider**
Headache	• Titrate more slowly • Decrease total dose, or decrease second dose • Evaluate other medications for cause/interaction
Nausea (with first dose)	• Advise participant to stay in bed after dose • Advise participants to consume small snack with dosing • Proceed with titration more slowly • Increase first dose (to shorten sleep onset latency), or decrease first dose • Set expectation for nausea to resolve over first 2 weeks
Nausea (in morning after waking)	• Advise participant to consume a small snack after waking • Proceed with titration more slowly • Decrease second dose, or take second dose earlier • Set expectation for nausea to resolve over first 2 weeks
Diarrhea	• Proceed with titration more slowly • Decrease total dose • Set expectation that diarrhea should resolve over first 2 weeks
Vomiting	• Advise participant to consume small snack with dosing • Set expectation that vomiting should resolve over first 2 weeks • Proceed with titration more slowly, and/or decrease total dose
Dizziness at bedtime	• Advise participant regarding avoidance of rapid postural changes • Advise participant to stay in bed after dose • Increase first dose (to shorten sleep onset time), or decrease first dose • Review concomitant medications and time of administration
Dizziness upon awakening	• Advise participant to stay in bed until dizziness subsides; avoid rapid postural changes • Decrease second dose and/or increase duration from second dose to waking • Review concomitant medications and time of administration
Enuresis	• Advise participant to urinate before bedtime and before taking second dose • Advise participant to restrict fluids before bedtime • Proceed with titration more slowly • Decrease total dose based on timing of enuresis
Decreased appetite and/or weight loss	• Decrease total dose • Monitor weight loss progression and clinical significance • Review concomitant medications
Parasomnias	• Proceed with titration more slowly (especially if prior history) • Ensure adequate time for sleep • Decrease first dose • Increase total dose • For idiopathic hypersomnia: Consider change from once- to twice-nightly

[a]Guidance provided for the trial was based on consensus guidance which was subsequently published in Morse AM, et al. Dosing Optimization of Low-Sodium Oxybate in Narcolepsy and Idiopathic Hypersomnia in Adults: Consensus Recommendations. *Neurol Ther.* 2024.13:785–807.[2] http://creativecommons.org/licenses/by-nc/4.0/.
LXB, low-sodium oxybate.