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Nocturnal Spontaneous Arousals in People With Narcolepsy and Idiopathic Hypersomnia Treated With Low-Sodium Oxybate

DUET STUDY 407

Chad M. Ruoff, MD[1]; David T. Plante, MD, PhD[2]; Deborah A. Nichols, MS[3]; Teresa L. Steininger, PhD[3]; Jing Dai, PhD[3]; M. Todd Kirby, PhD[4]; Sarah Akerman, MD[4]; Jessica K. Alexander, PhD[3]; Alessandra Milesi-Halle, MD, PhD[4]; Logan D. Schneider, MD[5]; Alyssa Cairns, PhD[4]

[1]Mayo Clinic, Scottsdale, AZ, USA; [2]University of Wisconsin–Madison, Madison, WI, USA; [3]Jazz Pharmaceuticals, Palo Alto, CA, USA; [4]Jazz Pharmaceuticals, Philadelphia, PA, USA; [5]Stanford University Center for Sleep Sciences and Medicine, Stanford, CA, USA.

Introduction

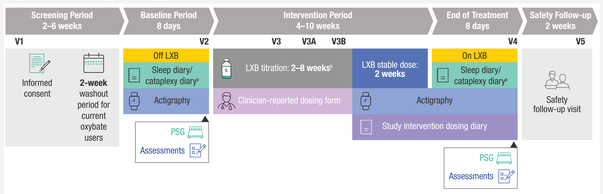
- Individuals with narcolepsy experience disrupted nighttime sleep, including increased arousals during sleep[1-3]
- Individuals with idiopathic hypersomnia often report nonrestorative nighttime sleep[4]; however, relatively few polysomnography (PSG) studies have been performed
  - While some studies have suggested that individuals with idiopathic hypersomnia have a lower arousal index (lower than individuals with narcolepsy or similar to controls),[4,5] others have demonstrated high arousal indices in idiopathic hypersomnia, similar to those observed in narcolepsy[5-7]
- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age or older with narcolepsy and the treatment of idiopathic hypersomnia in adults[8-11]
  - The impact of LXB on arousals in people with narcolepsy or idiopathic hypersomnia has not yet been evaluated
- 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) evaluating the effectiveness of LXB in treating daytime and nighttime symptoms, including polysomnography (PSG)-measured arousals, in participants with narcolepsy (type 1 [NT1] or 2 [NT2]) or idiopathic hypersomnia

Objective

- To evaluate the effect of LXB on PSG-determined arousals in individuals with narcolepsy or idiopathic hypersomnia

Methods

Figure 1. Study Design



***Ad libitum* PSG protocol**
- Bedtime was determined by habitual bedtime (same bedtime used for baseline and EOT visits)
- PSG was scheduled to allow a minimum of 10 hours time in bed, unless the participant naturally awakened earlier
- For logistical reasons, wake time must have occurred by noon (±15 minutes to avoid awakening from deep [stage N3] sleep)

[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. Investigator could optimize participant dosage and move to SDP at visit 3, 3A, or 3B but not during intervening weekly teleconferences.
BL, baseline; EOT, end of treatment; LXB, low-sodium oxybate; N3, non-rapid eye movement stage 3; PSG, polysomnography; SDP, stable-dose period; V, visit.

- DUET included a screening period (with a washout period for current oxybate users), a baseline (BL) period (participants were not on LXB), a titration period (participants began LXB treatment with individualized dosing adjustments to achieve their optimal dose), a stable-dose period (SDP; at optimal LXB dose), an end-of-treatment (EOT) period, and a safety follow-up
  - **Narcolepsy cohort:** all participants took LXB twice nightly (per US prescribing label)[8]
  - **Idiopathic hypersomnia cohort:** participants took a once- or twice-nightly LXB regimen based on the investigator's discretion (per US prescribing label)[8]
- At BL and EOT, participants underwent nocturnal PSGs using an *ad libitum* protocol to allow sufficient time in bed for a natural final awakening
  - PSG recordings were obtained according to standard protocol/montage and were centrally scored
  - During the EOT PSG, participants who were taking LXB twice nightly were awakened by the investigator to take the second dose; the participant was not awakened by the investigator during the BL PSG
    - At BL, a date/time for the first lights off and a final lights on were recorded
    - At EOT, the first LXB dose was taken and immediately after, a date/time for the first lights off was recorded; the participant was then awakened 3 hours 58 minutes after the first lights off, and the second LXB dose was taken prior to a second lights off 4 hours 0 minutes after the first lights off; a date/time for the final lights on at the natural awakening was recorded
  - Use of sleep-disordered breathing therapy (ie, for management of stable disease) was permitted
  - Arousals were defined as abrupt shifts in electroencephalogram frequency ≥3 seconds with ≥10 seconds of stable sleep preceding the change (per *The AASM Manual for the Scoring of Sleep and Associated Events* criteria)[12]
- Number of nocturnal arousals was a secondary endpoint for the narcolepsy cohort; other arousal- and respiratory-related endpoints for the narcolepsy and idiopathic hypersomnia cohorts were exploratory
  - Other arousal-related endpoints included the arousal index (events/hour of total sleep time [TST]), number of spontaneous arousals, respiratory-related arousals (those associated with hypopneas/apneas), and periodic limb movement (PLM)-related arousals
  - Respiratory and oximetry parameters, including apnea-hypopnea index (AHI) and mean oxygen saturation (SpO_2; monitored continuously by pulse oximetry throughout the PSG recording), were also assessed
  - All arousal, respiratory, and oximetry parameters were measured from first lights off to final lights on
- For all endpoints, least squares (LS) mean differences (95% confidence interval [CI]) at the EOT visit compared with BL visit were estimated using an analysis of covariance model adjusted for the BL value
  - *P* values were not adjusted for multiple comparisons and are considered nominal
- 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; 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

Figure 2. Key Inclusion and Exclusion Criteria

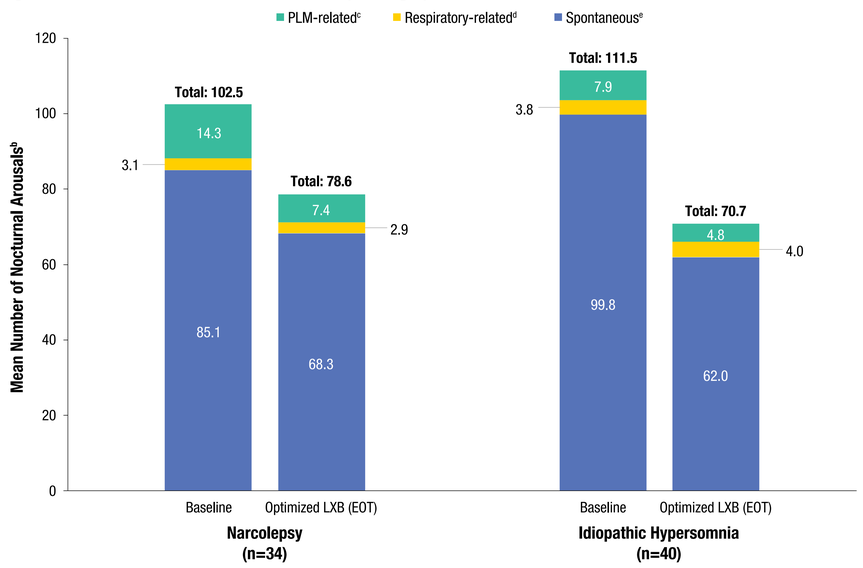
Key Inclusion Criteria
- 18–75 years of age with primary diagnosis of NT1 or NT2 (per ICSD-3 or DSM-5) or idiopathic hypersomnia (per ICSD-3)
- ESS score >10[a]
- Participants were allowed to continue taking concomitant anticataplectics or alerting agents, but must have been taking the same dosage for ≥1 month before screening visit 1 with no plan to adjust dosage during the study

Key Exclusion Criteria
- Untreated/inadequately treated sleep-disordered breathing (AHI >10)[b]
- History/presence of other untreated/inadequately treated sleep disorder or unstable/clinically significant medical condition, behavioral/psychiatric disorder, neurologic disorder, or surgical history that might affect participant's safety or interfere with study conduct
- Medication(s) contraindicated, with known drug-drug interaction, or similar EEG effects as LXB or medication(s) known to have clinically significant CNS sedating effects

[a]At screening visit 1 or if taking an oxybate medication at screening, at visit 2, after the washout period. [b]Hypopnea definition included a ≥4% desaturation per *The AASM Manual for the Scoring of Sleep and Associated Events*,[13] as assessed during baseline PSG visit.
AHI, apnea-hypopnea index; AASM, American Academy of Sleep Medicine; 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; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography.

Results

Figure 3. Total Number of Nocturnal Arousals (Full Night) Decreased from Baseline to End of Treatment[a]



[a]Completer analysis set. [b]Mean number of nocturnal arousals in total sleep time. [c]Mean number of arousals associated with a PLM in total sleep time. [d]Mean number of arousals associated with hypopneas/apneas in total sleep time. [e]Mean number of spontaneous arousals in total sleep time.
EOT, end of treatment; LXB, low-sodium oxybate; PLM, periodic limb movement.

- Mean number of total (ie, all) nocturnal arousals, as well as spontaneous and PLM-related arousals decreased from BL (not on LXB) to EOT (on optimized LXB) in both cohorts

Table 1. Baseline, End of Treatment, and Change in Nocturnal Arousals Overall and By Type (Full Night)[a]

	Narcolepsy (n=34)				Idiopathic Hypersomnia (n=40)			
Arousals	Baseline, mean (SE)	EOT, mean (SE)	LS mean Δ[b] (95% CI)	*P* value[c]	Baseline, mean (SE)	EOT, mean (SE)	LS mean Δ[b] (95% CI)	*P* value[c]
Total nocturnal arousals[d]	102.5 (9.3)	78.6 (8.7)	−23.9 (−39.3, −8.5)	0.0035	111.5 (9.0)	70.7 (6.9)	−40.8 (−52.7, −28.9)	<0.0001
Spontaneous[e]	85.1 (7.2)	68.3 (7.3)	−16.8 (−29.9, −3.7)	0.0133	99.8 (8.3)	62.0 (5.7)	−37.9 (−47.9, −27.8)	<0.0001
Respiratory-related[f]	3.1 (0.9)	2.9 (1.0)	−0.2 (−2.2, 1.9)	0.8618	3.8 (1.1)	4.0 (1.5)	0.1 (−2.1, 2.3)	0.9085
PLM-related[g]	14.3 (3.5)	7.4 (2.9)	−6.9 (−12.3, −1.5)	0.0136	7.9 (2.1)	4.8 (1.4)	−3.1 (−5.9, −0.3)	0.0310

[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal. [d]Mean number of all arousals in total sleep time. [e]Mean number of spontaneous arousals in total sleep time. [f]Mean number of arousals associated with hypopneas/apneas in total sleep time. [g]Mean number of arousals associated with a PLM in total sleep time.
BL, baseline; CI, confidence interval; EOT, end of treatment; LS, least squares; PLM, periodic limb movement; SE, standard error.

- From BL to EOT, a reduction in the mean number of all nocturnal, spontaneous, and PLM-related arousals was observed in participants with narcolepsy or idiopathic hypersomnia; mean number of respiratory-related arousals appeared stable

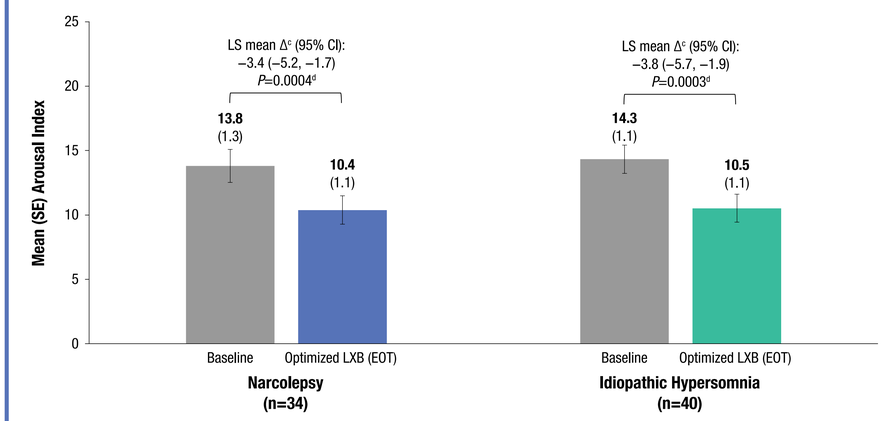
Table 2. Demographics and Baseline Characteristics[a,b]

Characteristic	Narcolepsy (N=55)	Idiopathic Hypersomnia (N=46)
Age (years), mean (SD)	33.4 (12.9)	38.1 (11.8)
Sex at birth, n (%)		
Male	15 (27.3)	9 (19.6)
Female	40 (72.7)	37 (80.4)
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[c]	1 (1.8)	1 (2.2)
Unknown	1 (1.8)	0
Body mass index (kg/m²), mean (SD)	29.5 (6.7)	28.5 (6.4)
Oxybate type at study entry, n (%)		
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
OSA diagnosis, n (%)	4 (7.3)	11 (23.9)
Concomitant alerting agent , n (%)[e,f,g]	31 (56.4)	19 (41.3)

[a]For additional demographic information, including concomitant alerting agent use, please see **Poster 393** and **Poster 413** for the narcolepsy and idiopathic hypersomnia cohorts, respectively. [b]Safety analysis set. [c]Participant reported >1 race. [d]No oxybate use within 2 weeks of entering the study. [e]Participants could have been taking multiple alerting medications. [f]Agents could have been prescribed for excessive sleepiness, idiopathic hypersomnia, and/or another condition. [g]Concomitant medications had a stop date on or after the date of the first dose of the study intervention or were ongoing.
OSA, obstructive sleep apnea; SD, standard deviation.

- A total of 16 (47.1%) participants with NT1 and 18 (52.9%) participants with NT2 were included in the completer analysis set (13 participants in the narcolepsy cohort transferred to a different study cohort - see **Poster 558**)
- A total of 40 participants with idiopathic hypersomnia were included in the completer analysis set

Figure 4. Arousal Index (Full Night) Decreased From Baseline to End of Treatment[a,b]



[a]Completer analysis set. [b]Events per hour of total sleep time. [c]Difference between EOT and BL. [d]*P* values reported are nominal.
CI, confidence interval; EOT, end of treatment; LS, least squares; LXB, low-sodium oxybate; SE, standard error.

Table 3. Respiratory and Oximetry Parameters (Full Night)[a]

	Narcolepsy (n=34)				Idiopathic Hypersomnia (n=40)			
Parameter	Baseline, mean (SE)	EOT, mean (SE)	LS mean Δ[b] (95% CI)	*P* value[c]	Baseline, mean (SE)	EOT, mean (SE)	LS mean Δ[b] (95% CI)	*P* value[c]
AHI (events/h)	1.9 (0.5)	1.8 (0.4)	−0.12 (−0.9, 0.7)	0.7611	1.4 (0.3)	2.0 (0.5)	0.7 (−0.2, 1.4)	0.1070
Mean SpO_2 (%)	95.4 (0.3)	95.6 (0.3)	0.2 (−0.2, 0.5)	0.2847	95.5 (0.2)	95.4 (0.2)	−0.1 (−0.5, 0.3)	0.4992

[a]Completer analysis set. [b]Difference between EOT and BL. [c]*P* values reported are nominal.
AHI, apnea-hypopnea index; BL, baseline; CI, confidence interval; EOT, end of treatment; h, hour; LS, least squares; PLM, periodic limb movements; SE, standard error; SpO_2, peripheral oxygen saturation.

- No significant differences were observed in AHI or mean SpO_2 between BL and EOT for both the narcolepsy and idiopathic hypersomnia cohorts

Table 4. Treatment-Emergent Adverse Events[a,b]

Participants, n (%)	Narcolepsy (N=55)	Idiopathic Hypersomnia (N=46)
With ≥1 TEAE	34 (61.8)	34 (73.9)
With ≥1 TEAE related to treatment	30 (54.5)	30 (65.2)
TEAEs occurring in ≥5% of participants		
Nausea	13 (23.6)	9 (19.6)
Dizziness	8 (14.5)	8 (17.4)
Headache	7 (12.7)	8 (17.4)
Somnolence	6 (10.9)	3 (6.5)
Vomiting	6 (10.9)	5 (10.9)
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)
Cough	3 (5.5)	2 (4.3)
Decreased appetite	3 (5.5)	3 (6.5)
Enuresis	3 (5.5)	3 (6.5)
Hypoesthesia	3 (5.5)	1 (2.2)
Middle insomnia	2 (3.6)	4 (8.7)

[a]For additional safety information, please see **Poster 393** and **Poster 413** for the narcolepsy and idiopathic hypersomnia cohorts, respectively. [b]Safety analysis set.
TEAE, treatment-emergent adverse event.

- In the narcolepsy cohort, no participants had a serious treatment-emergent adverse event (TEAE); 4 (7.3%) had a TEAE that led to study drug discontinuation (nausea, anxiety, dysphoria, and irritability)
- In the idiopathic hypersomnia cohort, 1 (2.2%) participant had a serious TEAE (hypoxia), and 1 (2.2%) participant had a TEAE that led to study drug discontinuation (depression; resolved after study drug discontinuation)
  - The serious TEAE of hypoxia (concurrent with influenza) was moderate in severity, determined to be unrelated to the study drug according to the investigator, and resolved

Conclusions

- Using an *ad libitum* PSG protocol, participants with narcolepsy or idiopathic hypersomnia taking open-label LXB experienced a lower number of nocturnal arousals and lower arousal index with LXB treatment compared with baseline
  - The reduced arousal index was due to a reduction in the number of spontaneous arousals and PLM-related arousals
  - These findings suggest that increased arousals may contribute to the nonrestorative sleep experienced by individuals with idiopathic hypersomnia[14-17]
- No worsening of respiratory and oximetry outcomes, including respiratory-related arousals, AHI, and mean SpO_2, with LXB treatment was observed in either cohort
- Limitations of the DUET study include 1) the open-label design and lack of a control group limit ability to attribute findings solely to LXB and 2) analyses were based on the completer analysis set of participants who reached a stable LXB dosage, which may not represent the experience of all individuals starting LXB treatment
- These findings support improvement of sleep disruption, adding to the improvements observed in other measures of sleep architecture with LXB in the narcolepsy and idiopathic hypersomnia cohorts (see **Posters 424** and **415**, respectively)

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Supplemental Statistical Methods

- For narcolepsy, formal hypothesis testing was conducted using the completer analysis set for the endpoints of Epworth Sleepiness Scale (ESS) score (decrease from baseline [BL]), total sleep stage shifts from N1/N2/N3/rapid eye movement [REM] to wake and N2/N3/REM to N1 (decrease from BL), duration of N3 sleep (increase from BL), and total number of nocturnal awakenings (decrease from BL).
- For idiopathic hypersomnia, formal hypothesis testing was conducted using the completer analysis set for the endpoints of ESS score (decrease from BL) and Idiopathic Hypersomnia Severity Scale total score (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.
- All reported endpoints 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.

Centralized Polysomnography Scoring Definitions:

- **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 Hz 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 >75 mV.
- **Stage R:** 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.
- **Arousal:** abrupt shift in electroencephalogram frequency, which may include theta, alpha, and/or frequencies >16 Hz but not spindles; the minimum duration of an arousal event is 3 seconds, with ≥10 seconds of stable sleep preceding the change; scoring arousals during REM must also be accompanied by a concurrent increase in submental electromyography lasting ≥1 second

More information on the DUET Study can be found in the following posters:

- Top-line results from the DUET study for narcolepsy and idiopathic hypersomnia cohorts presented in **Poster 393** and **Poster 413**, respectively
- Subjective sleep quality results for narcolepsy and idiopathic hypersomnia cohorts presented in **Poster 422** and **Poster 414**, respectively
- Sleep architecture for the narcolepsy cohort presented in **Poster 424**
- Sleep architecture for the idiopathic hypersomnia cohort in **Poster 415**
- Effectiveness and safety of LXB dosages >9 g/night in narcolepsy in **Poster 558**