003 Effectiveness and Optimization of Low-Sodium Oxybate in Participants With Narcolepsy Switching From High-Sodium Oxybate: Interim Data From the Substitution of Equal Grams of Uninterrupted Xyrem to Xywav (SEGUE) Study

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Introduction

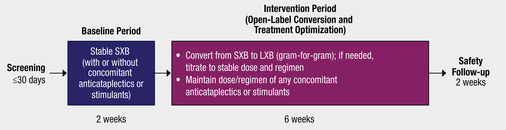
- High-sodium oxybate (SXB) is strongly recommended by the American Academy of Sleep Medicine for the treatment of narcolepsy due to its efficacy in improving cataplexy and excessive daytime sleepiness[1]
- Low-sodium oxybate (LXB) contains the same active moiety as SXB, with 92% less sodium, and is approved in the United States (US) for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and idiopathic hypersomnia in adults[2-6]
  - LXB has been recognized by the US Food and Drug Administration in the narcolepsy population for its greatly reduced chronic sodium burden compared with SXB, which is clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated[7]
- SEGUE (Substitution of Equal Grams of Uninterrupted Xyrem® to Xywav®) is an ongoing, phase 4, multicenter, open-label, single-arm study of safety, tolerability, effectiveness, and treatment optimization in participants with narcolepsy transitioning from SXB to LXB (NCT04794491)

Objective

- The primary objective of this study is to describe the clinical experience of participants switching from SXB to LXB for the treatment of narcolepsy with or without cataplexy
- An exploratory objective is to describe the ease of conversion and participant preference for LXB

Methods

Figure 1. SEGUE Study Design



LXB, low-sodium oxybate; SEGUE; Substitution of Equal Grams of Uninterrupted Xyrem® to Xywav®; SXB, high-sodium oxybate.

- Eligible participants are adults 18 to 80 years of age with narcolepsy type 1 or type 2 (based on criteria from the *International Classification of Sleep Disorders*, 3rd Edition[8] or *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition[9]) who have been taking a stable dose (maximum 9 g/night; no single dose >6 g) and regimen (once, twice, or thrice nightly) of SXB for ≥2 months, with or without additional anticataplectics or stimulants
- After 2 weeks on a stable SXB dose/regimen (baseline period), participants switch to the same dose (gram-for-gram) and regimen of LXB; any concomitant anticataplectics or stimulants are maintained at the current dose and regimen (intervention period; 6 weeks)
- Efficacy assessments include the Epworth Sleepiness Scale (ESS),[10] Patient Global Impression of Change (PGIc), a forced preference questionnaire (FPQ), and an ease of switching medication scale (EOSMS), all collected at the end of treatment or early discontinuation
  - Weekly cataplexy attacks were collected via diary for participants with narcolepsy type 1, but were not assessed as part of this interim analysis
- Treatment-emergent adverse events (TEAEs), as reported by participants, are collected until the end of the safety follow-up
- Results of an interim analysis (first 24 participants to complete or prematurely terminate the study) are reported

Results

Table 2. Exposure to SXB and LXB During the Baseline Period and Intervention Period

Parameter	SXB	LXB	
	Baseline Period	Start of Intervention Period	End of Intervention Period[a]
n	24	24	24[b]
Total nightly dose, g/night			
Mean (SD)	7.9 (1.8)	7.9 (1.8)	7.9 (1.8)
Median (min, max)	9.0 (2.3, 9.0)	9.0 (2.3, 9.0)	9.0 (2.3, 9.0)
Dosing regimen, n (%)			
Once nightly	2 (8.3)	2 (8.3)	2 (8.3)
Twice nightly	21 (87.5)	21 (87.5)	21 (87.5)
Thrice nightly	1 (4.2)	1 (4.2)	1 (4.2)

[a]End of treatment or early discontinuation. [b]Includes 1 participant who did not achieve a stable LXB dose/regimen.
LXB, low-sodium oxybate; max, maximum; min, minimum; SXB, high-sodium oxybate.

- Most participants continued taking LXB twice nightly and remained at a similar nightly dose for the duration of the study (maximum: 9 g/night), after switching from SXB to LXB gram-for-gram

Table 1. Baseline Demographics

Characteristic	Safety Population[a] (N=24)
Age, years	
Mean (SD)	45.5 (16.2)
Median (min, max)	43.5 (18, 74)
Sex, n (%)	
Male	11 (45.8)
Female	13 (54.2)
Race, n (%)	
Black or African American	2 (8.3)
White	22 (91.7)
Ethnicity, n (%)	
Hispanic or Latino	2 (8.3)
Non-Hispanic or Latino	22 (91.7)

[a]Includes all enrolled participants who took ≥1 dose of SXB after providing informed consent.
Max, maximum; min, minimum; SXB, high-sodium oxybate.

- Baseline demographics were similar to those reported in a prior real-world study of patients with narcolepsy taking SXB[11]

Table 3. Timing and Number of Changes to Stable LXB Dose and Regimen During the Intervention Period

Parameter	Safety Population[a] (N=24)
Participants who completed the intervention period, n (%)	
Yes	22 (91.7)
No[b]	2 (8.3)
Participants who achieved stable LXB dose and regimen, n (%)	
Yes[c]	23 (95.8)
Discontinued study early without reaching stable dose	1 (4.2)[d]
Time to achieve stable LXB dose and regimen[e,f], days	
n	23
Mean (SD)	1.4 (1.6)
Median (min, max)	1.0 (1, 8)
Number of changes required to achieve stable LXB dose and regimen	
n	23
Mean (SD)	0.1 (0.3)
Median (min, max)	0.0 (0, 1)
Never changed, n (%)	21 (91.3)
Changed once, n (%)	2 (8.7)

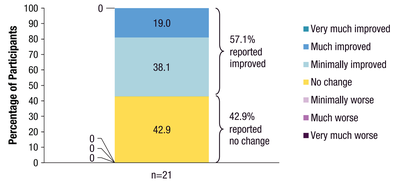
[a]Includes all enrolled participants who took ≥1 dose of SXB after providing informed consent. [b]Two participants discontinued during the intervention period. [c]Participants who completed the intervention period with LXB dose and regimen unchanged from week 6 of the study period or earlier to week 8 of the study period, or participants who discontinued from the intervention period with final LXB dose and regimen unchanged for ≥2 weeks. [d]Participant could not be optimized due to early termination from the study following a positive alcohol/urine screen. [e]Defined as the time from the first dose and regimen of LXB to the stable dose and regimen of LXB. [f]For participants who did not change their LXB dose and regimen, the minimum value (1 day) was noted.
LXB, low-sodium oxybate; max, maximum; min, minimum; SXB, high-sodium oxybate.

- Most participants (91%) did not modify dose or regimen after switching from SXB to LXB gram-for-gram

Figure 2. Responses on the PGIc, EOSMS, and FPQ at the End of the Intervention Period[a,b]

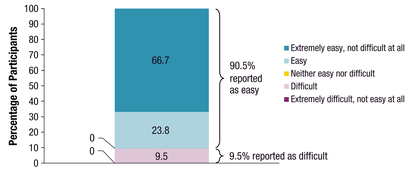
Patient Global Impression of Change (PGIc)

Please choose the response below that best describes the overall change in your narcolepsy since you started taking the study medication (XYWAV)



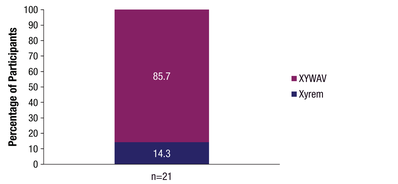
Ease of switching medication scale (EOSMS)

The process of switching to the new medication was:



Forced preference questionnaire (FPQ)

Thinking about your experience with Xyrem and XYWAV, which would you prefer to treat your narcolepsy?



[a]End of treatment or early discontinuation. [b]Includes participants with ≥1 PGIc, EOSMS, and FPQ assessment performed at the end of treatment or early discontinuation.
EOSMS, ease of switching medication scale; FPQ, forced preference questionnaire; LXB, low-sodium oxybate; PGIc, Patient Global Impression of Change; SXB, high-sodium oxybate.

- At the end of the intervention period, most participants reported improvement (much/minimal) or no change in narcolepsy symptoms on the PGIc, reported that the transition to LXB was easy (easy/extremely easy/not difficult at all) on the EOSMS, and preferred LXB over SXB on the FPQ

Table 4. Scores on the ESS at Baseline and the End of the Intervention Period

ESS Score	SXB	LXB
	Baseline (Day 1)	End of Intervention Period[a]
n	23	21
Mean (SD)	10.2 (5.2)	9.4 (5.5)
Median (min, max)	10.0 (2, 20)	7.0 (3, 23)

[a]Includes participants who completed the end of treatment or early discontinuation visit.
ESS, Epworth Sleepiness Scale; LXB, low-sodium oxybate; max, maximum; min, minimum; SXB, high-sodium oxybate.

- Scores on the ESS were numerically lower (improved) at the end of the intervention period compared to baseline; the average change was minimal (mean [SD] change, –0.6 [2.0]; median [range] change, 0.0 [–5, 3])

Table 5. Summary of TEAEs[a]

Category[b]	LXB
	Intervention Period
n	24[c]
Participants with ≥1 TEAE, n (%)	7 (29.2)
Mild	4 (16.7)
Moderate	1 (4.2)
Severe	1 (4.2)
Life threatening	1 (4.2)[d]
Participants with ≥1 TEAE related to study drug[e], n (%)	2 (8.3)
Participants with ≥1 serious TEAE, n (%)	1 (4.2)
Participants with ≥1 TEAE leading to discontinuation of study drug, n (%)	1 (4.2)
Participants with ≥1 TEAE leading to dose reduction of study drug, n (%)	1 (4.2)
Deaths, n (%)	0 (0)

[a]For SXB, a TEAE is defined as an AE that began or worsened before administration of the first LXB dose (ie, from screening through the end of the baseline period); for LXB, a TEAE is defined as an AE that began or worsened after administration of the first LXB dose (ie, from the start of the intervention period to the end of treatment; does not include the safety follow-up period). [b]Participants reporting >1 TEAE under a category are counted only once within that category. [c]Participants who took ≥1 dose of LXB. [d]Judged as not related to study drug by the investigator. [e]Judged as related by the investigator; TEAEs with a missing relationship to study drug are classified as related.
AE, adverse event; LXB, low-sodium oxybate; SXB, high-sodium oxybate; TEAE, treatment-emergent adverse event.

- The majority of TEAEs reported were mild to moderate during the intervention (LXB) period
  - One participant experienced a serious adverse event of hyperkalemia while taking LXB; this event was judged as not related to study drug by the investigator
    - In the phase 3 clinical trial of LXB in adults with narcolepsy, median changes from baseline in calcium, magnesium, potassium, and sodium were relatively minimal during the 16-week main study period, and no clinically meaningful trends were observed for electrolytes[2]
  - No TEAE was experienced by >1 participant during the same period; migraine was the only TEAE reported during both the screening/baseline and intervention periods
- There were no falls reported

Conclusions

- In this clinical study of participants with narcolepsy taking SXB, participants switched from SXB to LXB with minimal modifications of dose/regimen and reported that the transition process was easy
- Efficacy of oxybate treatment was maintained or improved, and most participants preferred LXB over SXB
- Most TEAEs reported were mild to moderate during the intervention (LXB) period

References: 1. Maski K, et al. *J Clin Sleep Med*. 2021;17:1881-93. **2.** Bogan RK, et al. *Sleep*. 2021;44:zsaa206. **3.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **4.** Szarfman A, et al. *N Engl J Med*. 1995;333(19):1291. **5.** US Food and Drug Administration. Clinical Review for Binosto, NDA 202344. 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **6.** 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. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **7.** US Food and Drug Administration. Clinical superiority findings. 2021. Available at: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. **8.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. Darien, IL: American Academy of Sleep Medicine; 2014. **9.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, DSM-5. Washington, DC: American Psychiatric Publishing; 2013. **10.** Johns MW. *Sleep*. 1991;14:540-5. **11.** Mayer G, et al. *Sleep*. 2018;41(9):zsy128.

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