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Impact of Switching From High- to Low-Sodium Oxybate on Ambulatory Blood Pressure in Patients With Narcolepsy

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Introduction

- Excess sodium intake, consumed by ≈90% of Americans, is strongly linked to elevated blood pressure (BP) and cardiovascular disease (CVD)[1-6]
- People living with narcolepsy are at increased risk for hypertension and CVD[7-11]
- Scientific bodies, qualified experts, and governments around the world recommend a total daily sodium intake upper limit of 2300 mg and a reduction (ie, from any amount) of ≥1000 mg/day (for most adults) to improve BP and heart health[1,12-17]
- High-sodium oxybate (SXB; Xyrem®) and low-sodium oxybate (LXB; Xywav®) are both approved by the US Food and Drug Administration to treat excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy; LXB is also approved to treat idiopathic hypersomnia in adults[18,19]
  - At the maximum prescribed adult nightly dose, SXB contains 71% of the recommended daily sodium intake[3,19]
  - LXB has the same active moiety as SXB but with 92% less sodium[7,18-23]

Table 1. Approximate Sodium Amounts at the Recommended Nightly Dosage of SXB or LXB

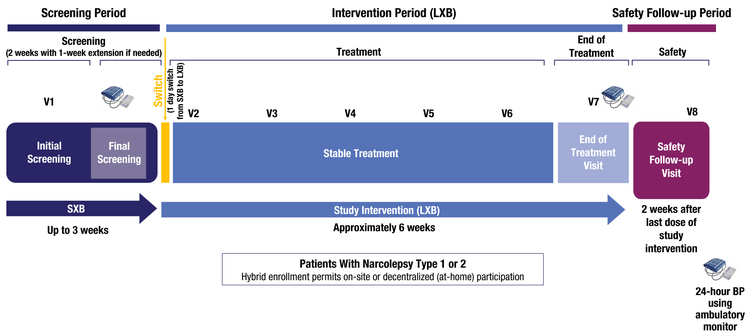
Oxybate	Recommended Adult Dosage	Sodium Amounts per Nightly Exposure
SXB[19]	6–9 g/night	1100–1640 mg
LXB[7,18,23]	6–9 g/night	87–131 mg

Objective

- XYLO (NCT05869773) evaluated changes in ambulatory and seated resting ("office") BP changes in study participants with narcolepsy after switching from twice-nightly SXB to LXB

Methods

Figure 1. Study Design



BP, blood pressure; LXB, low-sodium oxybate; SXB, high-sodium oxybate; V, visit.

- XYLO was an open-label, single-arm, multicenter, switch study conducted in the US and Europe, enrolling participants 18 to 70 years of age with narcolepsy (type 1 or 2) taking 6 to 9 g/night of SXB for ≥6 weeks at study entry
- A hybrid study design allowed enrollment either at an investigational site or virtually (decentralized; permitting in-person visits at home)
- Eligibility criteria included an average screening seated resting ("office") systolic blood pressure (SBP) between 130 and 155 mmHg (inclusive) and diastolic blood pressure (DBP) ≤95 mmHg (3 BP measurements at 1-minute intervals)
- Key exclusion criteria:
  - Resistant hypertension, defined as controlled BP and treated with ≥4 antihypertensive medications or uncontrolled BP despite concurrent use of ≥3 antihypertensive medications of different classes that included a diuretic
  - History or presence of significant CV or kidney (ie, renal impairment with creatinine clearance <45 mL/min) disease or any significant CV condition that, in the investigator's opinion, could jeopardize participant safety in the study
- Following a screening/baseline period (up to 3 weeks), participants switched to LXB (same dosage/regimen) for ≈6 weeks and subsequently completed an end-of-treatment (EOT) visit and a safety follow-up visit (≥14 days after the last dose of LXB); the total study duration was approximately 11 weeks for each participant
- The primary endpoint was change from baseline (SXB) to EOT (LXB) in mean 24-hour ambulatory SBP
- Key secondary endpoints were change from baseline (SXB) to EOT (LXB) in mean daytime ambulatory, seated resting ("office"), and mean nighttime ambulatory SBP
- Exploratory endpoints included changes in mean 24-hour ambulatory, daytime ambulatory, seated resting ("office"), and nighttime mean DBP, and change in 24-hour urinary sodium
- Additional details on statistical analyses can be found in the supplemental material, available by scanning the QR code in the lower right corner of the poster

Results

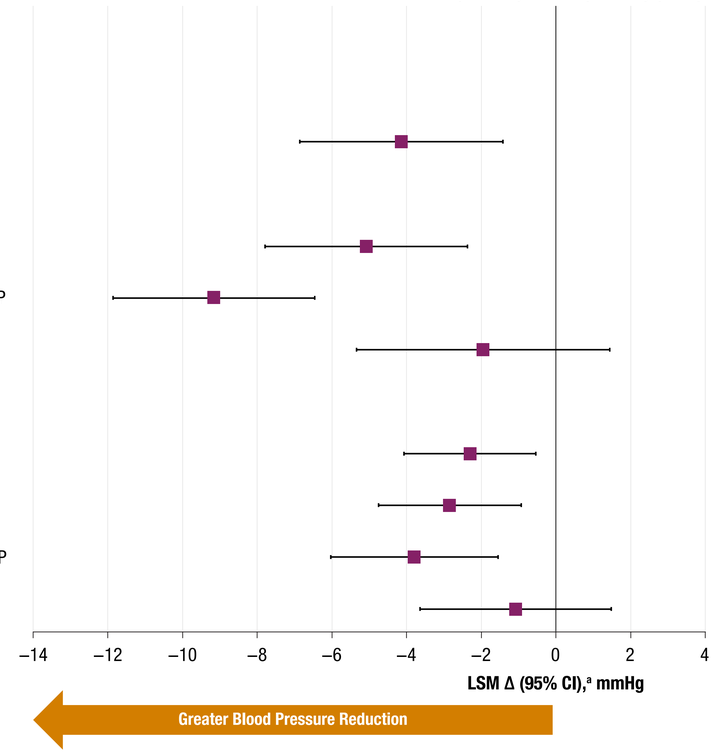
Table 2. Demographic and Baseline Characteristics (Completer Population)

Parameter	Overall (N=43)
Age, years, mean (SD)	45.0 (11.3)
Female, n (%)	28 (65.1)
Race, n (%)	
White	37 (86.0)
Black or African-American	3 (7.0)
Asian	1 (2.3)
Unknown	2 (4.7)
Ethnicity, n (%)	
Hispanic or Latino	3 (7.0)
Not Hispanic or Latino	40 (93.0)
BMI,[a] kg/m², mean (SD)	30.3 (7.5)
Seated resting ("office") SBP at screening, mmHg, mean (SD)	138.0 (5.7)
Seated resting ("office") DBP at screening, mmHg, mean (SD)	85.2 (6.6)
Use of antihypertensive medications, n (%)	14 (32.6)
Narcolepsy type, n (%)	
Type 1	21 (48.8)
Type 2	22 (51.2)

[a]Sample size with BMI data was 41.
BMI, body mass index; DBP, diastolic blood pressure; EOT, end of treatment; LXB, low-sodium oxybate; SBP, systolic blood pressure; SD, standard deviation.

- Per the prespecified study design, 43 participants with valid EOT 24-hour ambulatory SBP recordings were analyzed; mean age was 45 years, 65% were female, 86% were White, and 33% were on stable antihypertensives

Figure 2. Clinically Meaningful Blood Pressure Reductions Were Observed From Baseline (on SXB) to EOT (on LXB) (Completer Population)

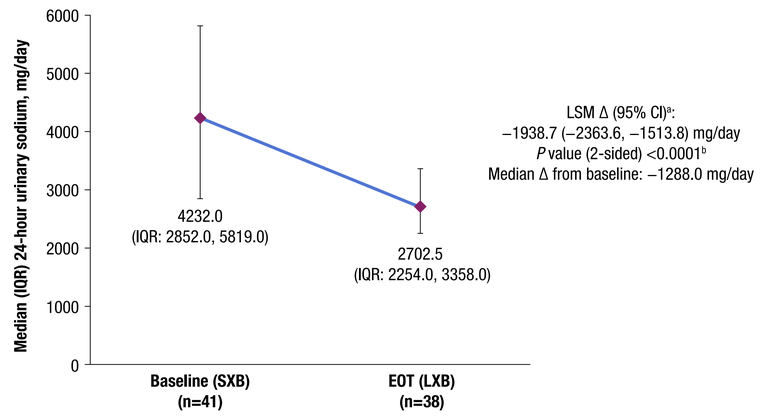


	BL (SXB) (N=43)	EOT (LXB) (N=43)	LSM Δ (95% CI),[a] mmHg	*P* value 1-sided	*P* value 2-sided
	Mean (SE), mmHg				
Primary Endpoint					
24-hour ambulatory SBP	132.3 (1.8)	128.2 (1.8)	−4.1 (−6.9, −1.4)	0.0019*	0.0038
Secondary Endpoints					
Daytime ambulatory SBP	139.1 (1.9)	134.1 (1.9)	−5.1 (−7.8, −2.4)	0.0003*	0.0005
Seated resting ("office") SBP	138.0 (0.9)	128.8 (1.4)	−9.2 (−11.9, −6.5)	<0.0001*	<0.0001
Nighttime ambulatory SBP	116.9 (2.1)	114.9 (2.4)	−2.0 (−5.3, 1.4)	0.1265	0.2530
Exploratory Endpoints					
24-hour ambulatory DBP	77.3 (1.6)	75.0 (1.4)	−2.3 (−4.1, −0.5)		0.0118[b]
Daytime ambulatory DBP	82.7 (1.6)	79.8 (1.5)	−2.8 (−4.8, −0.9)		0.0045[b]
Seated resting ("office") DBP	85.2 (1.0)	81.4 (1.5)	−3.8 (−6.0, −1.6)		0.0014[b]
Nighttime ambulatory DBP	65.2 (1.8)	64.1 (1.9)	−1.1 (−3.6, 1.5)		0.3993[b]

The marker is the LSM change, and the error bars indicate the 95% CI.
[a]Baseline-adjusted change in BP from BL (on SXB) to EOT (on LXB). [b]*P* values are nominal. *Indicates statistical significance.
BL, baseline; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; EOT, end of treatment; LSM, least squares mean; LXB, low-sodium oxybate; SBP, systolic blood pressure; SE, standard error; SXB, high-sodium oxybate.

- LSM (95% CI) change in 24-hour ambulatory SBP (primary endpoint) was −4.1 (−6.9, −1.4; *P*=0.0019) mmHg, achieving the interim (75%) prespecified efficacy stopping criteria
- The proportion of participants with office SBP <130 mmHg at baseline was 0% (per eligibility criteria) and increased to 47% at EOT; the proportion of participants with 24-hour ambulatory SBP <130 mmHg also increased from baseline (35%) to EOT (56%)

Figure 3. Reductions in 24-Hour Urinary Sodium From Baseline (on SXB) to EOT (on LXB) Paralleled Reduced Sodium Intake (Completer Population)



The marker is the median; error bars indicate IQR.
[a]Baseline-adjusted change from baseline (on SXB) to EOT (on LXB). [b]*P* value is nominal.
CI, confidence interval; EOT, end of treatment; IQR, interquartile range; LSM, least squares mean; LXB, low-sodium oxybate; SE, standard error; SXB, high-sodium oxybate.

- Mean (SD) total SXB and LXB dosages were 8.0 (1.1) and 8.1 (1.1) g/night, respectively, representing a mean (SD) sodium content of 1456.5 (206.2) and 117.8 (16.3) mg (mean [SD] difference of 1338.8 [190.7] mg sodium)

Table 3. Treatment-Emergent Adverse Events (Safety Population)

Parameter, n (%)	Overall (N=61)
TEAE	20 (32.8)
Mild	16 (26.2)
Moderate	4 (6.6)
Severe	0
Life-threatening	0
Fatal	0
TEAE related to study drug	9 (14.8)
Serious TEAE	0
Participants with ≥1 TEAE leading to discontinuation of LXB	0
Participants with ≥1 TEAE leading to dose change of LXB	0
Common TEAEs (occurring in ≥1 participant)	
Upper respiratory tract infection	3 (4.9)
Dysgeusia	2 (3.3)
Nausea	2 (3.3)
Vomiting	2 (3.3)

LXB, low-sodium oxybate; TEAE, treatment-emergent adverse event.

- Adverse events occurred in 32.8% of participants in the safety population
  - All adverse events were mild or moderate in severity; all adverse events considered related to the study drug were mild in maximum severity
  - No serious adverse events occurred

Conclusions

- Switching from SXB to LXB in the XYLO study reduced daily treatment-related sodium intake by mean (SD) of 1338.8 (190.7) mg, which was paralleled by 24-hour urinary sodium reduction and associated with clinically meaningful reductions in 24-hour ambulatory and seated resting ("office") SBP
- Limitations of XYLO include the open-label, single-arm design
- Reducing sodium intake from medications has important implications for BP, consistent with the robust and well-established published body of evidence on dietary and medication-related sodium reduction[1-4,12,13,24-28]
- Given the increased risk and burden of CV conditions for people with narcolepsy,[7-11] these BP results help inform individuals living with narcolepsy and their healthcare providers when assessing oxybate treatment options

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Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Under the direction of the authors, Peloton Advantage, LLC (an OPEN Health company), employees Kalpana Vijayan, PhD, and Stephanie Phan, PharmD, provided medical writing support and an editor provided editorial support for this poster, which were funded by Jazz Pharmaceuticals.

Disclosures: VK Somers is a consultant for Jazz, ApniMed, Axsome, iRhythm, Mineralys, and Lilly, and serves on the Sleep Number Scientific Advisory Board. **RJ Kovacs** is a consultant to Jazz and Eli Lilly. He serves on data and safety monitoring boards for Immunovant and Relmada and on Clinical Events Committees for Cook and Zydus. **JK Alexander, C Baranak, DA Nichols, J Dai,** 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. **S Akerman** is a former full-time employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **A Ajayi** is a consultant to Jazz Pharmaceuticals. He has participated in Scientific and marketing advisory boards for Jazz Pharmaceuticals and Avadel. Dr Ajayi has been a site principal investigator for narcolepsy and studies sponsored by Jazz Pharmaceuticals, Avadel, Takeda, Harmony Biosciences, and Centessa. **B Hutchinson** is a consultant to Jazz Pharmaceutical and CardioOne. **Y Dauvilliers** is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, Centessa, Avadel, Idorsia, Takeda, Harmony Biosciences, and Bioprojet. **WB White** is a cardiovascular safety consultant to 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 Methods

- Statistical analyses
  - A 2-stage group sequential design with an adaptive sample size was used, targeting a sample size of 57 completers for 90% power to detect a mean decrease in 24-hour SBP of 3.5 mmHg with a standard deviation of 8.0 mmHg from baseline (SXB) to EOT (LXB)
  - An interim analysis was planned after 43 (75%) participants completed a valid 24-hour ambulatory SBP recording at the EOT visit after 6 weeks of LXB and the study recruitment would end if the primary endpoint significance level (O'Brien-Fleming one-sided alpha level of 0.00998) was met
  - Least squares mean (LSM), 95% confidence interval (CI), and *P* values were obtained from an analysis of covariance model of the change for each endpoint from the baseline to the EOT, adjusted for the baseline value
  - To account for multiplicity secondary to multiple endpoints, a fixed hierarchical testing method was prespecified and tested sequentially for change in mean SBP following 6 weeks of LXB after switching from SXB in the following order: 24-hour ambulatory SBP, daytime ambulatory SBP, seated resting ("office") SBP, and nighttime ambulatory SBP; other endpoints were not adjusted for multiplicity and are therefore considered nominal
  - One-sided *P* values were reported for baseline-adjusted SBP LSM (95% CI) changes
  - Two-sided *P* values were reported for baseline-adjusted DBP and 24-hour urinary sodium LSM (95% CI) changes
- Study populations:
  - **Completer population:** all participants who completed a valid (ie, meeting minimal data standards) 24-hour ambulatory BP recording at the EOT visit after 6 weeks of LXB
  - **Safety population:** all participants who took ≥1 dose of LXB