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Design Elements for a Switch Study From High- to Low-Sodium Oxybate Evaluating Blood Pressure in Narcolepsy (XYLO)

XYLO
A BLOOD PRESSURE STUDY FOR PEOPLE WITH NARCOLEPSY

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Introduction

- Excess sodium intake can elevate blood pressure (BP), potentially increasing the risk of cardiovascular (CV) disease, stroke, myocardial infarction, and CV mortality[1-5]
- People with narcolepsy have a high burden of CV comorbidities and CV event risk even before consideration of additional medication-specific CV risks[6-8]
- The American College of Cardiology/American Heart Association (ACC/AHA) recommends that individuals with, or at risk of developing, CV disease aim for a total daily sodium intake of <1500 mg[9]
  - In addition to dietary sodium, high sodium–containing medications can contribute substantially to daily sodium intake[10,11]
- High-sodium oxybate (SXB; Xyrem®) is recommended for treating narcolepsy,[12] yet starting on SXB is associated with increased risk of new-onset hypertension or antihypertensive medication initiation in these patients[13]
  - When taken at the recommended dose of 6–9 g/night, SXB contains 1100–1640 mg of sodium per night[14]
- Low-sodium oxybate (LXB; Xywav®), which has the same active moiety as SXB but 92% less sodium, is approved by the US Food and Drug Administration to treat excessive daytime sleepiness or cataplexy in patients ≥7 years of age with narcolepsy and idiopathic hypersomnia in adults[14-18]
  - LXB at the recommended dose of 6–9 g/night contains 87–131 mg of sodium per night[15,19]

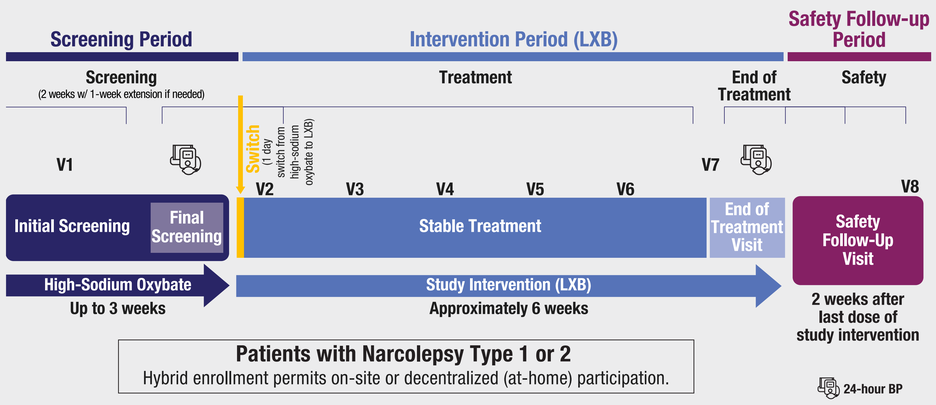
Objective

- XYLO (NCT05869773) will evaluate the impact of switching from SXB to LXB on 24-hour ambulatory and seated (in-clinic or at-home) systolic BP (SBP) in participants with narcolepsy

Methods

- XYLO is an open-label, multicenter, switch study enrolling participants 18–70 years of age with narcolepsy (type 1 or 2) taking 6–9 g/night of SXB for ≥6 weeks at study entry (**Figure 1**)
- XYLO's hybrid study design provides both on-site and decentralized enrollment options for participants; decentralized participants are monitored at home by mobile health professionals

Figure 1. Study Design



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

- Participant eligibility is shown in **Table 1**
- Following a 2- to 3-week screening period on a stable SXB dose/regimen, participants will transition to the same dose/regimen of LXB for 6 weeks during the intervention period
- The primary endpoint of XYLO is change from baseline to end of treatment (EOT; at 6 weeks) in mean 24-hour ambulatory SBP (**Table 2**)
- Secondary endpoints include changes from baseline to EOT in mean daytime and mean nighttime SBP derived from the ambulatory BP monitor, and the changes from baseline to EOT in mean seated (in-clinic or at-home) SBP (**Table 2**)
- Exploratory endpoints include correlation between changes in 24-hour mean SBP and changes in 24-hour urine sodium excretion (**Table 3**)
- Safety endpoints will be collected throughout the study (**Table 3**)

Table 1. Enrollment Eligibility Criteria

Key Inclusion Criteria

- Male or female 18–70 years of age (inclusive)
- Documented diagnosis of narcolepsy type 1 or 2 meeting ICSD-3 or DSM-5 criteria
- Taking a dose of high-sodium oxybate (SXB) of 6–9 g/night (inclusive) divided into 2 doses for ≥6 consecutive weeks before screening
- Medications known to affect BP (including stimulants, WPAs, and antihypertensives) must be at the same dosing regimen for ≥2 months before screening and maintained at that dose
- Average screening SBP (3 measures at 1-minute intervals) between 130–145 mmHg (inclusive)
- Average screening DBP (3 measures at 1-minute intervals) ≤95 mmHg

Key Exclusion Criteria

- History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect participant safety or interfere with study assessments
- History or presence of significant CV disease or any significant CV condition that in the investigator's opinion may jeopardize participant safety in the study
- Presence of atrial fibrillation detected on screening ECG
- Current or recent (within the past 2 years) diagnosis of a moderate or severe substance use disorder (excluding caffeine or nicotine if the nicotine use does not impact sleep)
- Calculated creatinine clearance <45 mL/minute
- Occupation requiring nighttime or variable shift work

BP, blood pressure; CV, cardiovascular; DBP, diastolic blood pressure; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ECG, electrocardiogram; ICSD-3, *International Classification of Sleep Disorders, Third Edition*; SBP, systolic blood pressure; WPA, wake-promoting agent.

Table 2. Primary and Secondary Endpoints

Objective	Domain	Endpoint
Primary	24-hour ambulatory SBP	• Change from baseline to end-of-treatment in 24-hour average SBP
Secondary	Daytime ambulatory SBP	• Change from baseline to end-of-treatment in daytime average SBP
	Seated resting SBP	• Change from baseline to end-of-treatment in seated resting average SBP
	Nighttime ambulatory SBP	• Change from baseline to end-of-treatment in nighttime average SBP

SBP, systolic blood pressure.

Table 3. Exploratory and Safety Endpoints

Objective	Domain/Description
Exploratory	• Ambulatory DBP • Seated resting DBP • Day-night BP decline (dipping) • Relationship between SBP and urine sodium excretion • Participant-reported change in conditions[a] • Participant-reported change in severity of conditions[a]
Safety	• Additional safety endpoints relating to TEAEs will also be collected

[a]Includes diaphoresis, nocturia, edema, and enuresis.
BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; TEAE, treatment-emergent adverse event.

- A target sample size of 57 completers will enable 90% power to detect a mean decrease in 24-hour SBP of 3.5 mmHg with a standard deviation of the difference of 8.0 mmHg, from baseline to the end of treatment
  - Statistical significance will be determined using a one-sided alpha level of 0.025
- Using a 2-stage group sequential design, the sample size will be adaptively determined; an interim analysis at 75% completion will inform the final study sample size
- The use of ambulatory BP monitoring in single-arm studies reduces potential for observer bias in assessing BP and reduces the effect of temporary fluctuations in BP associated with clinic BP (ie, "white coat effect")[20]
- Dietary salt intake is not monitored or restricted as part of this study, similar to a real-world context; correlations between urinary sodium excretion and SBP will be employed to examine changes at each assessment and between timepoints
- Participants are asked to maintain consistent sleeping habits, dietary habits, and exercise regimens to avoid confounding effects on BP

Conclusions

- XYLO is the first clinical study to investigate the effect of transitioning to LXB from SXB on 24-hour SBP in people with narcolepsy
- Limitations of XYLO are its open-label design and lack of a control arm/condition, which could lead to investigator and participant bias
- In light of the association between high sodium intake and CV disease,[1-5] and the high burden and increased risk of CV disease in people with narcolepsy,[6-8] this study will help inform healthcare provider and patient selection of optimal treatment for narcolepsy

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