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Novel Design Elements to Evaluate Sleep Architecture and Outcomes in an Idiopathic Hypersomnia and Narcolepsy Study

DUET STUDY 407

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Introduction

- Low-sodium oxybate (LXB, Xywav®) is approved by the US Food and Drug Administration (FDA) for the treatment of idiopathic hypersomnia in adults and the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age or older with narcolepsy[1-4]
- The efficacy and safety of LXB in the treatment of idiopathic hypersomnia and narcolepsy are well established,[5-8] but opportunities remain to better understand the association of LXB with sleep architecture and other daytime and nighttime outcomes that are important to patients and clinicians
- Jazz DUET (**D**evelop hypersomnia **U**nderstanding by **E**valuating low-sodium oxybate **T**reatment; NCT05875974) is a phase 4, prospective, multicenter, single-arm, open-label interventional study evaluating the association of LXB with excessive daytime sleepiness, polysomnography (PSG) sleep parameters, and functional outcomes in adults with idiopathic hypersomnia and adults with narcolepsy type 1 or 2
- An expert advisory board was convened to gather input regarding key study design elements

Objective

- Describe the input sought from an expert advisory board, and the incorporation of novel elements into the design of a patient-centric study evaluating the association of LXB with daytime and nighttime symptoms in idiopathic hypersomnia and narcolepsy

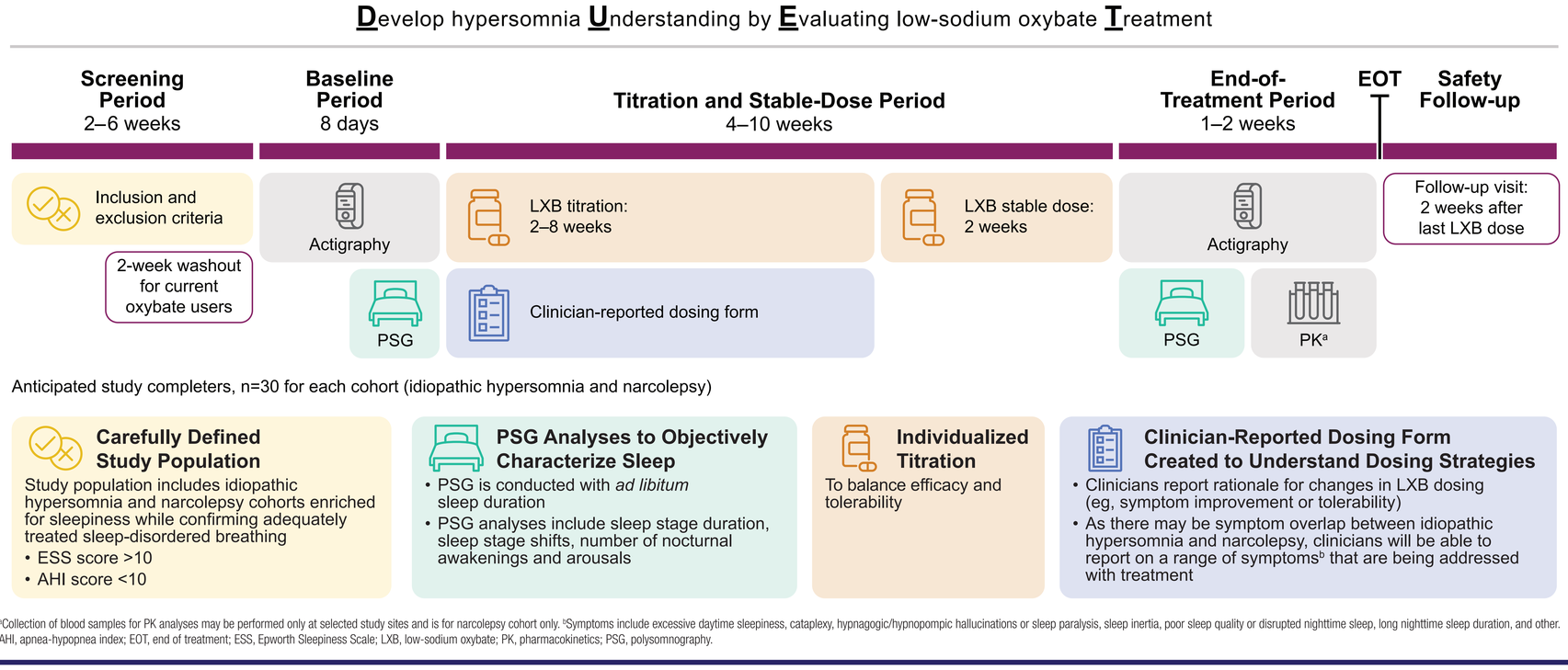
Methods

- Advisors were 6 clinicians with expertise in treating patients with idiopathic hypersomnia and narcolepsy and/or expertise in PSG
- Expert advisors completed a premeeting survey and then attended a 4-hour advisory board meeting with the study sponsor
- Four main topics were discussed:
  - Eligibility criteria for multiple cohorts
  - Optimization of assessments/endpoints to improve participant experience
  - Newly created materials for capturing individualized dosing information during titration
  - Clinically meaningful analyses that are important to clinicians and patients
- In addition, a patient advisory board provided feedback on the number and scheduling of assessments to ensure that an unreasonable burden was not being placed on study participants, and identified outcomes that were most important from a patient perspective (see Abstract 1106/Poster 304)

Results

- DUET includes a screening period (with a washout for participants taking an oxybate medication at study entry), a baseline period (off oxybate treatment), a titration period (for individualized LXB dosing adjustments based on participants' needs), a stable-dose period, an end-of-treatment period (taking an optimized stable dose of LXB), and a safety follow-up
- Eligibility criteria were designed to be generalizable to real-world settings, while excluding medical conditions related to patient safety or factors that may confound scientific objectives
- The study population includes participants currently taking oxybate medications, participants who took oxybate medications in the past, and participants who are naive to oxybate
- The following exclusion criterion was defined to allow participants with comorbid yet adequately treated sleep-disordered breathing to enroll in the study:
  - Evidence of untreated or inadequately treated sleep-disordered breathing, defined as apnea-hypopnea index >10 (US Centers for Medicare & Medicaid Services rules), during baseline visit PSG
- This study was designed to allow the investigators to optimize each participant's dosage based on the investigator's clinical judgment. To meet this objective, expert advisors provided feedback on the following materials:
  - A clinician titration guidance document was created to provide titration guidelines based on feedback from an expert consensus panel. However, the individualized titration period (2–8 weeks) was designed to allow for dosing optimization based on the investigator's clinical judgment
  - A clinician-reported dosing form was created to capture details of the treatment regimen and reasons for dosing changes at each titration step in order to better understand the clinician's rationale for dose modifications and to confirm the participant's optimized dosage
- Baseline characteristics of DUET study participants with idiopathic hypersomnia are described in Abstract 1332/Poster 432; baseline characteristics of participants with narcolepsy are described in Abstract 1337/Poster 437

Figure 1. Novel Elements in Final DUET Study Design



[a]Collection of blood samples for PK analyses may be performed only at selected study sites and is for narcolepsy cohort only. [b]Symptoms include excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations or sleep paralysis, sleep inertia, poor sleep quality or disrupted nighttime sleep, long nighttime sleep duration, and other.
AHI, apnea-hypopnea index; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LXB, low-sodium oxybate; PK, pharmacokinetics; PSG, polysomnography.

Table 1. Key Assessment Descriptions

Assessment	Description
Actigraphy	Activity profile measured with wrist-worn device that records movement, light, and temperature with outputs that include total sleep time and other measures related to sleep and daytime activity patterns
Cataplexy diary[a]	Daily electronic diary assessing change in weekly rate of cataplexy attacks; participant records number of daily cataplexy attacks (0 if none)
Clinician-reported dosing form	Clinician questionnaire designed to capture details of the treatment regimen for each titration step, as well as reasons for changes, in order to better understand the clinician's dosing rationale and confirm the participant's optimized dose
ESS	Sleep propensity in daily life; 8 items scored on 4-point scale (0 [would never doze] to 3 [high chance of dozing]); higher scores associated with excessive daytime sleepiness
IHSS[b]	Severity and functional consequences of idiopathic hypersomnia symptoms; 14 rated items include symptoms of excessive sleepiness, sleep inertia, long sleep duration; total score, 0–50
PGIc	Patient impression of change: 3 separate questions on change in sleep inertia, fatigue, and overall symptoms after treatment, with each question rated on 7-point Likert-type scale from 1 (very much improved) to 7 (very much worse)
PGIs	Patient impression of severity: 3 separate questions on severity of sleep inertia, fatigue, and overall symptoms, with each question rated on 7-point Likert-type scale from 1 (not present) to 7 (extremely severe)
PK parameters[c]	Includes maximum plasma concentration (C_{max}) and area under the concentration–time curve from 0 to infinity ($AUC_{0-\infty}$)
PSG	Recording of physiological electrodes during sleep; scored to describe sleep architecture, percentage and duration of sleep stages, sleep stage shifts, nocturnal awakenings and arousals, and other measures
Sleep diary	Daily electronic diary assessing nightly sleep patterns and quality, degree of feeling rested or refreshed on awakening, and if night was atypical (eg, holiday)
Study intervention participant dosing diary	Electronic diary capturing stable dosage, doses/night, g/dose; dosage modifications and explanations of changes included

[a]Only participants with narcolepsy type 1. [b]Idiopathic hypersomnia cohort only. [c]Narcolepsy cohort only.
$AUC_{0-\infty}$, area under the concentration–time curve from 0 to infinity; C_{max}, maximum plasma concentration; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; PGIc, Patient Global Impression of Change; PGIs, Patient Global Impression of Severity; PK, pharmacokinetics; PSG, polysomnography.

Table 2. Objectives and Endpoints

Objective	Domain	Endpoint	
		Idiopathic Hypersomnia	Narcolepsy
Primary	Excessive daytime sleepiness	• ESS total score	• ESS total score
Secondary	Patient-reported symptom severity and functional outcomes	• IHSS total score • PGIc and PGIs (overall, sleep inertia, fatigue) • Sleep diary (level of feeling rested/refreshed on awakening)	• PGIc and PGIs (overall, sleep inertia, fatigue) • Sleep diary (level of feeling rested/refreshed on awakening)
	Safety[a]	• Incidence and severity of AEs • C-SSRS	• Incidence and severity of AEs • C-SSRS
	PK	N/A	• PK parameters[b,c]
	PSG	N/A	• Number of stage shifts[d] • Duration and percentage of N1, N2, N3, and REM sleep • Number of nocturnal arousals • Number of nocturnal awakenings

[a]Data from additional safety-related measures were collected for patients in the PK cohort. [b]Only participants with narcolepsy who complete a PK visit.
[c]PK parameters including but not limited to C_{max} and $AUC_{0-\infty}$. [d]Number of stage shifts from N1, N2, N3, and REM sleep to wake and from N2, N3, and REM sleep to N1 sleep.
AE, adverse event; $AUC_{0-\infty}$, area under the concentration–time curve from 0 to infinity; C_{max}, maximum plasma concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; N/A, not applicable; N1, N2, N3, non–rapid eye movement sleep stage; PGIc, Patient Global Impression of Change; PGIs, Patient Global Impression of Severity; PK, pharmacokinetics; PSG, polysomnography; REM, rapid eye movement.

Conclusions

- DUET is a phase 4 patient-centric study with a design informed by both clinician/scientific experts and a patient advisory board
- DUET is the first prospective evaluation of changes in sleep architecture (PSG) associated with open-label LXB treatment in adults with idiopathic hypersomnia or narcolepsy
- DUET is limited by the absence of a placebo group for comparison
- Results from DUET will provide patients and clinicians with additional information regarding the association of LXB with nighttime and daytime symptomatology

References: 1. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **2.** Szarfman A, et al. *N Engl J Med.* 1995;333(19):1291. **3.** US Food and Drug Administration. Clinical review for Binosto, NDA 202344. 2012. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. **4.** 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. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. **5.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21(1):53-65. **6.** Bogan RK, et al. *Sleep.* 2021;44(3):zsaa206. **7.** Thorpy MJ, et al. *Nat Sci Sleep.* 2022;14:1901-1917. **8.** Morse AM, et al. *J Clin Sleep Med.* 2023;19(10):1811-1822.

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