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Efficacy of Lower-Sodium Oxybate in the Treatment of Idiopathic Hypersomnia: Evaluation of Response Based on the Idiopathic Hypersomnia Severity Scale Score

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Introduction

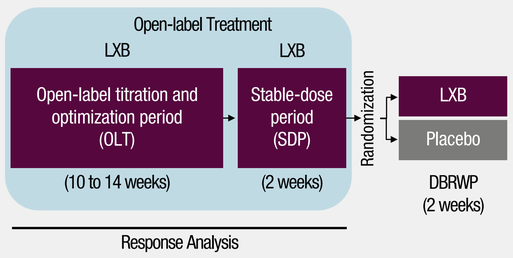
- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by excessive daytime sleepiness (EDS), with sleep inertia and prolonged nighttime sleep as key symptoms[1]
- Lower-sodium oxybate (LXB; Xywav®) is the first United States (US) Food and Drug Administration (FDA)-approved treatment for idiopathic hypersomnia, and is also approved to treat cataplexy or EDS in patients 7 years of age and older with narcolepsy[2]
- The efficacy and safety of LXB for the treatment of idiopathic hypersomnia were established in a phase 3, double-blind, randomized withdrawal study (NCT03533114), in which change in the Idiopathic Hypersomnia Severity Scale (IHSS) was a key secondary efficacy endpoint[3]
  - The IHSS is a 14-item self-reported questionnaire (0–50 score range; higher scores indicate greater severity) that assesses key symptoms of idiopathic hypersomnia[4]
  - An IHSS total score ≤22 was established as the appropriate cutoff value for discriminating between untreated patients with idiopathic hypersomnia and controls[4]
  - The meaningful within-person change (MWPC) of the IHSS score between untreated and treated patients is 4 points[5]

Objective

- This post hoc analysis evaluated response to LXB treatment over time on IHSS scores during an open-label period of this phase 3 clinical study[4]

Methods

Figure 1. Study Design

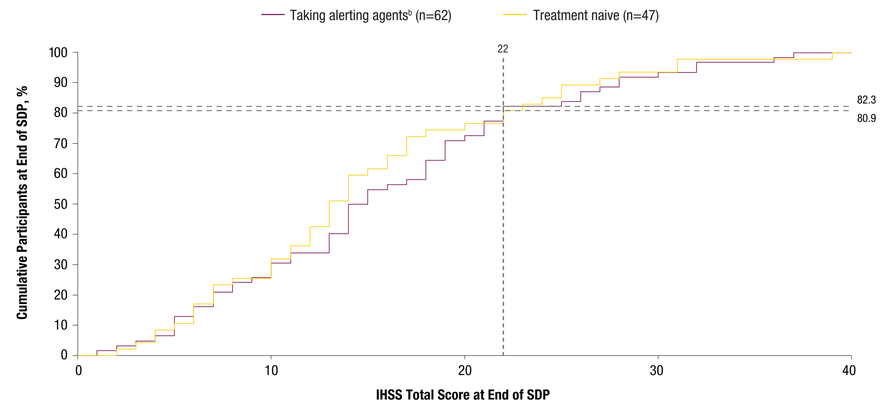


DBRWP, double-blind randomized withdrawal period; LXB, lower-sodium oxybate.

- Eligible participants were adults (18–75 years of age) with a primary diagnosis of idiopathic hypersomnia according to *International Classification of Sleep Disorders*, 2nd Edition (ICSD-2)[6] or ICSD-3[1] criteria and an average nocturnal total sleep time of at least 7 hours, including participants with and without long sleep time
- Participants were either treatment naive or were taking medications for idiopathic hypersomnia symptoms, including alerting agents (stimulants or wake-promoting agents; on a stable regimen) and/or sodium oxybate (SXB; Xyrem®)
- Participants began LXB treatment and were titrated to an optimal dose during an open-label titration and optimization period (OLT; 10–14 weeks); they then remained on their individually optimized LXB dose during a 2-week, open-label, stable-dose period (SDP)
- The IHSS was completed at baseline; during OLT weeks 1, 4, and 8; at end of OLT; and at end of SDP
- For this post hoc analysis, remission was defined as IHSS total score ≤22,[4] and response was defined as a decrease from baseline in total IHSS score of ≥4 points[5] with open-label LXB treatment
- Participants treated with SXB at study entry (n=6) had a mean (SD) IHSS score at baseline of 15.1 (7.1) and were not included in this analysis, which focused on the effects of oxybate in SXB-naive participants

Results

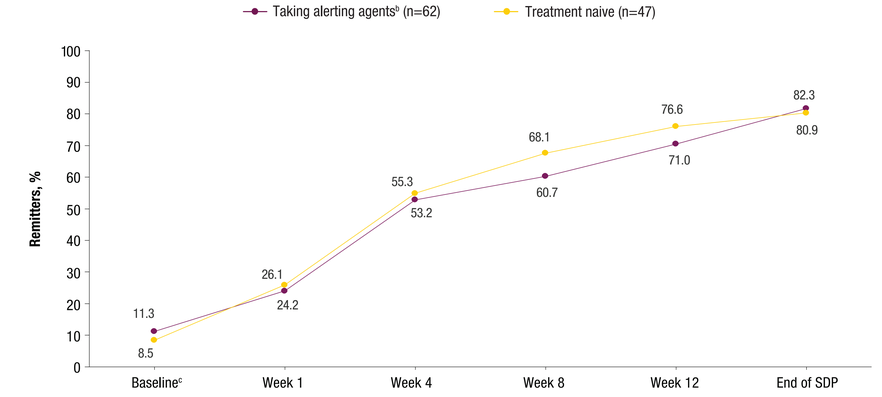
Figure 2. Over 80% of Participants Achieved IHSS Total Score of ≤22 Points (Remission)[a]



IHSS, Idiopathic Hypersomnia Severity Scale; SDP, stable-dose period.
[a]Modified intent-to-treat population includes all participants who took at least 1 dose of double-blind study drug and had at least 1 post-randomization set of efficacy assessments. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.
[b]Not including the 6 participants taking sodium oxybate at study entry at study entry, all of whom had IHSS score ≤22 points at baseline.

- IHSS total score ≤22 points was achieved by end of SDP in 82.3% of participants taking alerting agents and 80.9% of treatment-naive participants

Figure 3. Time Course of Remission (IHSS Total Score of ≤22 Points)[a]



IHSS, Idiopathic Hypersomnia Severity Scale; SDP, stable-dose period.
[a]Modified intent-to-treat population includes all participants who took at least 1 dose of double-blind study drug and had at least 1 post-randomization set of efficacy assessments. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.
[b]Not including participants taking sodium oxybate at study entry.
[c]Refers to the day study drug is dispensed.

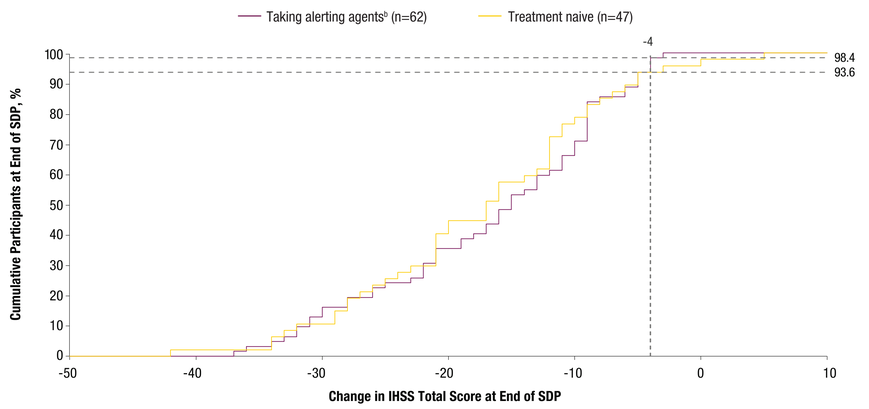
Table 1. Demographics and Baseline Disease Characteristics (Safety Population)[a]

Characteristic	Taking Alerting Agents (n=82)	Treatment Naive[b] (n=66)	Safety Population (N=148)
Age, years, mean (SD)	40.8 (13.0)	39.4 (14.3)	40.2 (13.5)
Female, n (%)	62 (75.6)	40 (60.6)	102 (68.9)
Race, n (%)			
White	74 (90.2)	53 (80.3)	127 (85.8)
Black or African American	5 (6.1)	4 (6.1)	9 (6.1)
Other	3 (3.7)	9 (13.6)	12 (8.1)
Baseline IHSS score, mean (SD)	33.0 (7.0)	32.4 (7.6)	32.7 (7.2)

IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; SXB, sodium oxybate.
[a]Safety analysis population includes all participants who took at least 1 dose of study drug; participants taking SXB at study entry (n=6) are excluded.
[b]Includes participants not taking SXB or an alerting agent (stimulant or wake-promoting agent) at study entry.

- The mean (SD) total nightly dose of LXB during SDP was 6.8 (1.7) g in participants taking alerting agents at study entry and 6.3 (1.8) g in treatment-naive participants

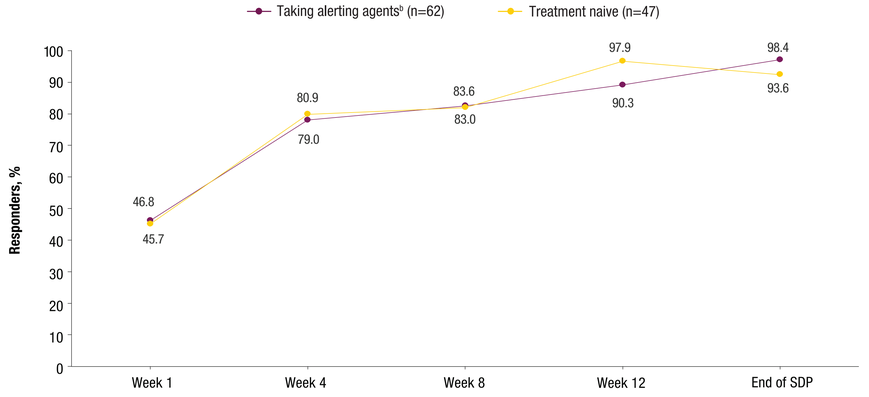
Figure 4. Over 90% of Participants Responded to LXB Treatment With IHSS Total Score Decrease of ≥4 Points[a]



IHSS, Idiopathic Hypersomnia Severity Scale; LXB, lower-sodium oxybate; SDP, stable-dose period.
[a]Modified intent-to-treat population includes all participants who took at least 1 dose of double-blind study drug and had at least 1 post-randomization set of efficacy assessments. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.
[b]Not including participants taking sodium oxybate at study entry.

- IHSS total score decrease of ≥4 points was achieved by end of SDP in 98.4% of participants taking alerting agents and 93.6% of treatment-naive participants

Figure 5. Time Course of Response in Participants With IHSS Total Score Decrease of ≥4 Points[a]



IHSS, Idiopathic Hypersomnia Severity Scale; SDP, stable-dose period.
[a]Modified intent-to-treat population includes all participants who took at least 1 dose of double-blind study drug and had at least 1 post-randomization set of efficacy assessments. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.
[b]Not including participants taking sodium oxybate at study entry.

- Treatment-emergent adverse events (reported by ≥10% of total participants across all study periods, excluding placebo data) included nausea (22.1%), headache (17.5%), dizziness (12.3%), anxiety (11.0%), and vomiting (11.0%)

Conclusions

- Over 80% of participants achieved remission of their idiopathic hypersomnia symptoms, based upon the IHSS total score cutoff value for discriminating between untreated patients with idiopathic hypersomnia and controls (≤22 points)
  - Over half of participants achieved remission by week 4, and the proportion of participants who achieved remission increased over the duration of the open-label period
- Up to 98% of participants demonstrated a clinically meaningful response to treatment (reduction in IHSS total score of ≥4 points)
  - Approximately half of participants demonstrated a clinically meaningful response to treatment by week 1, and the proportion of participants who demonstrated a clinically meaningful response increased over the duration of the open-label period
- The safety profile of LXB was consistent with that observed in narcolepsy

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. **2.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals. **3.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21:53-65. **4.** Dauvilliers Y, et al. *Neurology.* 2019;92:e1754-e62. **5.** Rassu AL, et al. *J Clin Sleep Med.* 2022;18:617-29. **6.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic & Coding Manual.* 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

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Disclosures: Y Dauvilliers is a consultant for and has participated in advisory boards for Jazz Pharmaceuticals, UCB Pharma, Flamel Technologies, Theranexus, and Bioprojet. **A Chen, T Steininger,** and **W Macfadden** 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. **R Rosenberg** has received consultancy fees from Eisai; honoraria from Merck; research funding from Jazz Pharmaceuticals, Merck, Actelion, Eisai, and Philips Respironics; and has served on the speakers' bureau for Merck and as a board member for Jazz Pharmaceuticals.

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