134

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

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Introduction

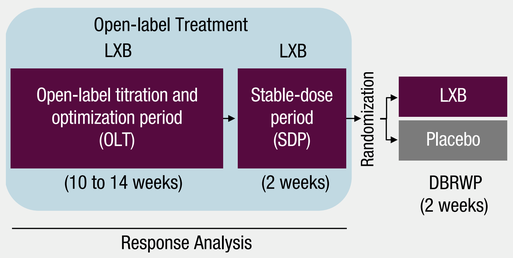
- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by excessive daytime sleepiness (EDS), with sleep inertia and prolonged nighttime sleep as key symptoms[1]
- Lower-sodium oxybate (LXB; Xywav®) is the first United States (US) Food and Drug Administration (FDA)-approved 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 Epworth Sleepiness Scale (ESS) was the primary efficacy endpoint[3]
  - The ESS is an 8-item self-report questionnaire (0–24 score range; higher scores indicate greater EDS)
  - An ESS total score ≤10 is considered normal[4]
  - A minimum within-person change (MWPC) to identify a treatment response in narcolepsy has been defined as a decrease of ≥2 points[5]; an MWPC in idiopathic hypersomnia has not been established
- A variety of criteria for treatment response have been used in studies in narcolepsy[6-11] or pooled analyses of studies in narcolepsy and obstructive sleep apnea,[12,13] including ESS score reduction of 3, 4, or more points[6,7,11,12]; ESS score reduction of 12%, 20% to 25%, or approximately 38%[8-10,12,13]; or attainment of ESS total score ≤10[6,7,11,13]

Objective

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

Methods

Figure 1. Study Design

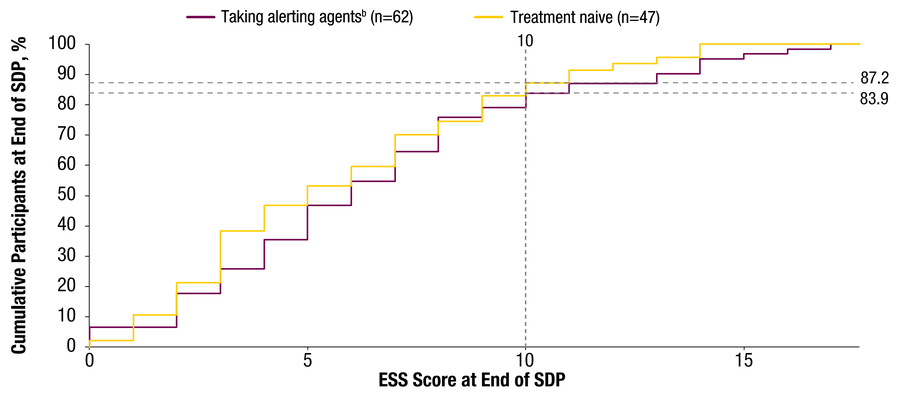


DBRWP, double-blind randomized withdrawal period; LXB, lower-sodium oxybate.

- 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)[14] 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 ESS 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 ESS total score ≤10,[6,7,11,13] and response was defined as decrease from baseline in total ESS score of ≥4 points[12] with open-label LXB treatment
- Participants treated with SXB at study entry (n=6) had a mean (SD) ESS score at baseline of 5.7 (4.9) and were not included in this analysis, which focused on the effects of oxybate in SXB-naive participants

Results

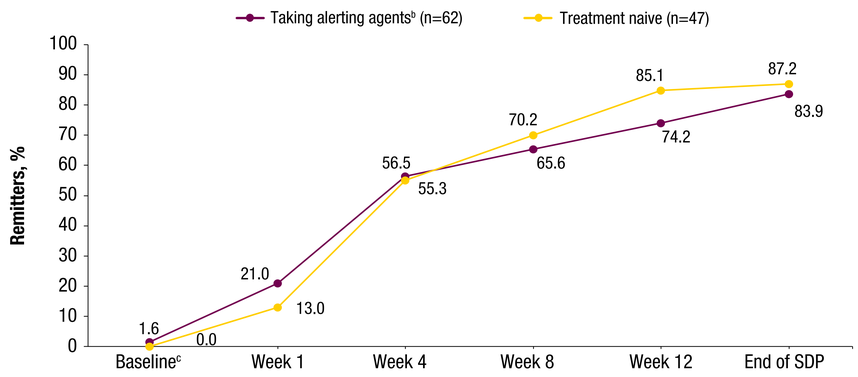
Figure 2. Over 80% of Participants Achieved ESS Score of ≤10 Points (Remission) by End of SDP[a,b]



ESS, Epworth Sleepiness 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. [b]Not including the 6 participants taking sodium oxybate at study entry, of whom 5 (83.3%) had ESS score ≤10 points at baseline. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.

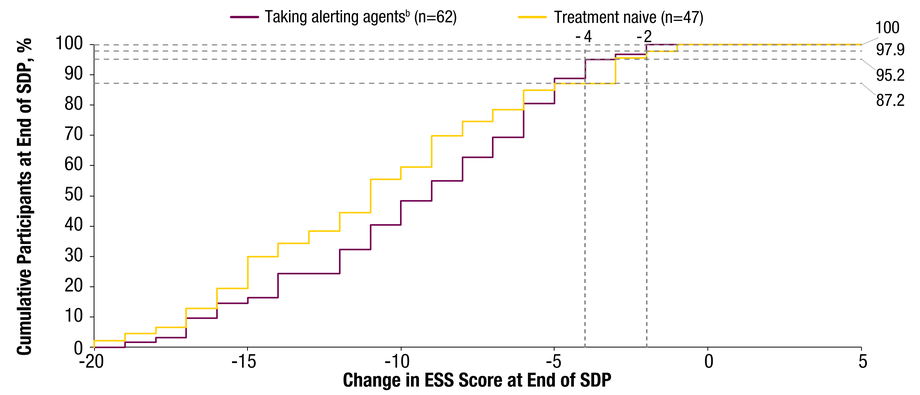
- By end of SDP, ESS score of ≤10 points was achieved in 83.9% of participants taking alerting agents and 87.2% of treatment-naive participants

Figure 3. Time Course of Remission (ESS Score ≤10 Points)[a]



ESS, Epworth Sleepiness 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. [b]Not including the 6 participants taking sodium oxybate at study entry, of whom 5 (83.3%) had ESS score ≤10 points at baseline. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria. [c]Refers to the day study drug is dispensed.

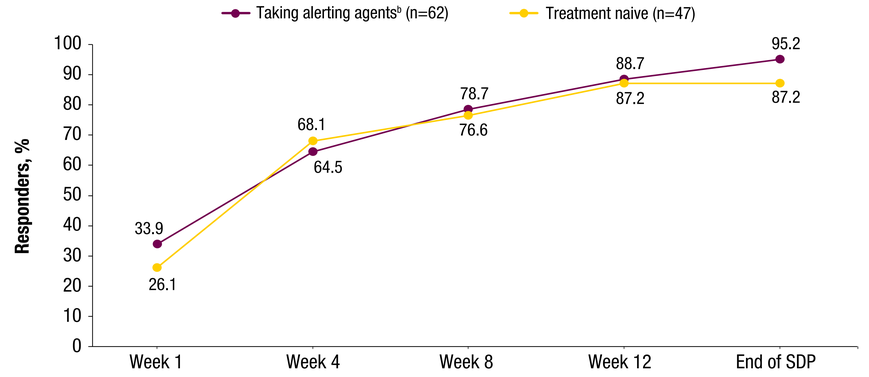
Figure 4. Over 85% of Participants Responded to LXB Treatment With ESS Score Decrease of ≥4 Points[a]



ESS, Epworth Sleepiness 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. [b]Not including the 6 participants taking sodium oxybate at study entry. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.

- By end of SDP, ESS score decrease of ≥4 points was achieved in 95.2% of participants taking alerting agents and 87.2% of treatment-naive participants, and ESS score decrease of ≥2 points was achieved in 100% of participants taking alerting agents and 97.9% of treatment-naive participants

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



ESS, Epworth Sleepiness 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. [b]Not including the 6 participants taking sodium oxybate at study entry. Eight participants discontinued due to lack of efficacy or because they did not meet randomization criteria.

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 ESS score, mean (SD)	16.4 (2.9)	16.7 (2.7)	16.5 (2.8)

ESS, Epworth Sleepiness 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

- 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 excessive daytime sleepiness, based upon the ESS total score established for normal individuals (≤10 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 95% of participants demonstrated a clinically meaningful response to treatment (decrease in total ESS score of ≥4 points)
  - Approximately two-thirds of participants demonstrated a clinically meaningful response to treatment by week 4, 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.** Johns MW. *Sleep*. 1991;14:540-5. **5.** Maski K, et al. *J Clin Sleep Med*. 2021;17:1895-945. **6.** Dauvilliers Y, et al. *Sleep*. 2019;42(11):zsz174. **7.** Davis CW, et al. *Sleep Med*. 2021;81:210-7. **8.** Steffen AD, et al. *J Sleep Res*. 2018;27:e12628. **9.** Bogan RK, et al. *J Clin Sleep Med*. 2015;11:427-32. **10.** Scrima L, et al. *Sleep Med*. 2017;38:108-12. **11.** Meskill GJ, et al. *CNS Drugs*. 2022;36:61-9. **12.** Lammers GJ, et al. *Sleep Med*. 2019;64(suppl 1):S210. **13.** Rosenberg R, et al. *J Clin Sleep Med*. 2021;17:711. **14.** 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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