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Efficacy of Lower-Sodium Oxybate in Participants With Idiopathic Hypersomnia: Results From the Open-label Treatment Phase of a Clinical Study

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Nancy Foldvary-Schaefer, DO, MS[1]; Michael J. Thorpy, MD[2]; Abby Chen, MS[3]; Wayne Macfadden, MD[4]; Yves Dauvilliers, MD, PhD[5,6]

[1]Sleep Disorders Center, Department of Neurology, Cleveland Clinic, Cleveland, OH, USA; [2]Albert Einstein College of Medicine, Bronx, NY, USA; [3]Jazz Pharmaceuticals, Palo Alto, CA, USA; [4]Jazz Pharmaceuticals, Philadelphia, PA, USA; [5]Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France; [6]University of Montpellier, INSERM Institute Neuroscience Montpellier (INM), Montpellier, France

Introduction

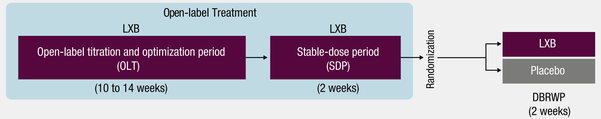
- Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by excessive daytime sleepiness (EDS), with severe sleep inertia and prolonged nighttime sleep as key symptoms commonly reported by patients[1]
  - The symptoms of idiopathic hypersomnia may partially overlap with those of psychiatric disorders,[2] and psychiatric symptoms and comorbidities occur frequently in patients with idiopathic hypersomnia[3]
- Lower-sodium oxybate (LXB) is the first United States Food and Drug Administration–approved treatment for idiopathic hypersomnia, and is also approved to treat cataplexy or EDS in patients 7 years of age and older with narcolepsy[4]
- The efficacy and safety of LXB for the treatment of idiopathic hypersomnia were established in a phase 3, double-blind, randomized withdrawal study (NCT03533114)[5]

Objective

- This post hoc analysis evaluated efficacy of LXB during the open-label titration and optimization and stable-dose periods in participants with idiopathic hypersomnia who were either treatment naive or were taking alerting agents at study entry

Methods

Figure 1. Study Design[a]



DBRWP, double-blind randomized withdrawal period; LXB, lower-sodium oxybate.
[a]The study also included a screening period (14 to 30 days), open-label safety extension period (OLE; 24 weeks), and safety follow-up period. Data from the OLE have been presented elsewhere.[6]

- 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)[7] or ICSD-3[1] criteria
  - Although not used in the eligibility criteria for the present study, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition[8] contains diagnostic criteria for idiopathic hypersomnia under the term "hypersomnolence disorder"

Table 1. Diagnostic Criteria for Idiopathic Hypersomnia (ICSD-3)

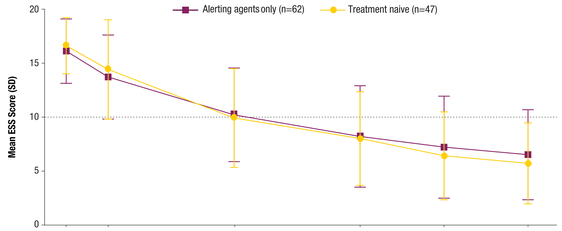
Idiopathic Hypersomnia[1]
A. The patient has excessive daytime sleepiness
B. Cataplexy is absent
C. An MSLT shows <2 sleep onset REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was ≤15 min
D. The presence of at least 1 of the following: 1. MSLT sleep latency of ≤8 min 2. Total 24-h sleep time ≥660 min (typically 12–14 h) on 24-h polysomnographic monitoring
E. Insufficient sleep syndrome is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy)
F. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications

ICSD-3, *International Classification of Sleep Disorders*, 3rd Edition; MSLT, multiple sleep latency test; REM, rapid eye movement.

- Participants were either treatment naive or were taking medications for idiopathic hypersomnia symptoms, including alerting agents (stimulants or wake-promoting agents) and/or sodium oxybate (SXB)
  - Participants taking alerting agents were required to have an Epworth Sleepiness Scale (ESS) score ≥11 at entry, and to have been taking the same dose and regimen for ≥2 months before screening and to take the same dose throughout the study
  - Participants taking SXB at study entry (n=6) were excluded from these post hoc efficacy analyses
- The ESS was completed at baseline; during open-label titration and optimization period (OLT) weeks 1, 4, and 8; at end of OLT; and at end of stable-dose period (SDP)
  - The ESS is an 8-item self-report questionnaire (0–24 score range; higher scores indicate greater EDS)
- The Idiopathic Hypersomnia Severity Scale (IHSS) was completed at baseline; during OLT weeks 1, 4, and 8; at end of OLT; and at end of SDP
  - The IHSS is a 14-item self-report questionnaire (0–50 score range; higher scores indicate greater severity) that assesses key symptoms of idiopathic hypersomnia and functional impairments associated with those symptoms
- The Patient Global Impression of Change (PGIc) was completed during OLT weeks 1, 4, and 8; at end of OLT; and at end of SDP
  - The PGIc is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse)

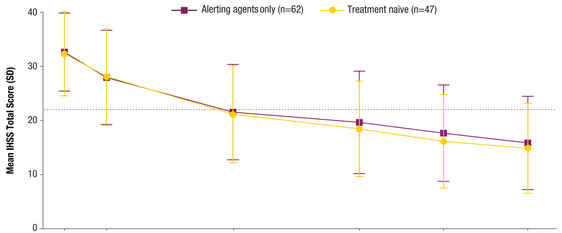
Results

Figure 2. ESS Scores Decreased During Open-label Treatment in Both Groups (mITT Population)[a,b]



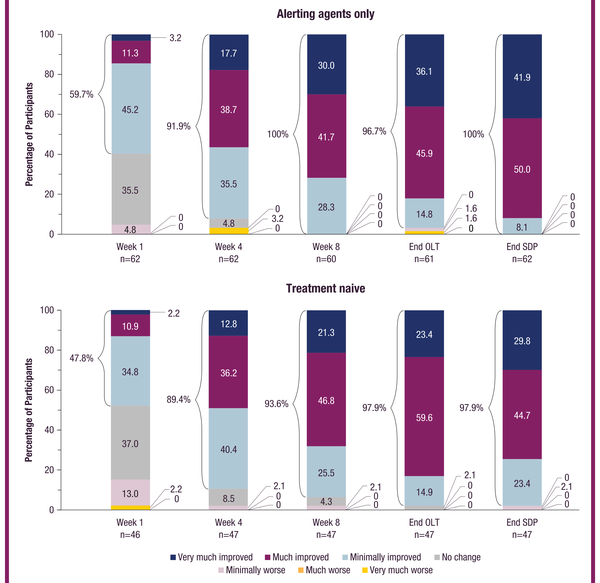
The dashed line indicates the maximum normal ESS score; ESS scores >10 represent pathological sleepiness.[9]
ESS, Epworth Sleepiness Scale; mITT, modified intention-to-treat; OLT, open-label treatment titration and optimization period; SDP, stable-dose period; SXB, sodium oxybate.
[a]Modified intent-to-treat 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]Excludes 6 participants taking SXB at study entry.

Figure 3. IHSS Scores Decreased During Open-label Treatment in Both Groups (mITT Population)[a,b]



The dashed line indicates the maximum normal IHSS score. An IHSS total score <22 was established as the appropriate cutoff value for discriminating between untreated patients with idiopathic hypersomnia and controls.[10]
IHSS, Idiopathic Hypersomnia Severity Scale; mITT, modified intention-to-treat; OLT, open-label treatment titration and optimization period; 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]Excludes 6 participants taking SXB at study entry.

Figure 4. PGIc Scores Improved During Open-label Treatment in Both Groups (mITT Population)[a]



mITT, modified intention-to-treat; OLT, open-label treatment titration and optimization period; PGIc, Patient Global Impression of Change; SDP, stable-dose period.
[a]Analysis includes safety population (participants who received ≥1 dose of study drug).

- Over 90% of participants reported improvement on the PGIc at end of SDP; over 70% reported they were "much improved" or "very much improved"

Table 2. Demographics and Baseline Disease Characteristics (Safety Population)

Characteristic	Taking Medication for Idiopathic Hypersomnia at Baseline[a] (n=82)	Treatment Naive[b] (n=66)	Safety Population[c] (N=148)
Age, 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[d]	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)
Baseline IHSS score, mean (SD)	33 (7.0)	32.4 (7.6)	32.7 (7.2)

ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; SD, standard deviation; SXB, sodium oxybate.
[a]Includes participants who were taking an alerting agent (stimulant or wake-promoting agent) at study entry; excludes participants taking SXB at study entry (n=6).
[b]Includes participants not taking SXB or an alerting agent (stimulant or wake-promoting agent) at study entry.
[c]Includes all participants who took at least 1 dose of study drug; excludes participants taking SXB at study entry (n=6).
[d]Includes declined to state.

- Participants included in the post hoc efficacy analysis (modified intent-to-treat population) were treatment naive (n=47) or were taking alerting agents (either traditional stimulants or wake-promoting agents) at study entry (n=62)

- Treatment-emergent adverse events (TEAEs; 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%)
- Most TEAEs were mild or moderate in severity; 1 (0.6%) participant experienced ≥1 severe TEAE. Across all study periods (excluding placebo data), 4 (2.6%) participants experienced ≥1 serious adverse event. No deaths were reported

Conclusions

- Overall, participants with idiopathic hypersomnia taking open-label LXB demonstrated substantial improvements relative to baseline on the ESS, IHSS, and PGIc, whether taking alerting agents or treatment naive at study entry
- Baselines ESS and IHSS scores for participants taking alerting agents were similar in severity to those who were treatment naive, emphasizing the ineffectiveness of many current treatments
- 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.** Dauvilliers Y, et al. *BMC Med.* 2013;11:78. **3.** Saad R, et al. Presented at: Annual Meeting of the Associated Professional Sleep Societies; June 10-13, 2021. **4.** XYWAV® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. **5.** Dauvilliers Y, et al. *Lancet Neurol.* 2022;21:53-65. **6.** Foldvary-Schaefer N, et al. Presented at: Annual Meeting of the American Academy of Neurology; April 2-7, 2022. **7.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic & Coding Manual*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005. **8.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*. Washington, DC: American Psychiatric Publishing; 2013. **9.** Johns MW. *Sleep*. 1991;14(6):540-545. **10.** Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762.

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