REVITALYZ: A Phase 3, Double-Blind, Placebo-Controlled, Randomised Withdrawal Trial of Extended-Release Sodium Oxybate for Idiopathic Hypersomnia

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INTRODUCTION

- Idiopathic hypersomnia (IH) is a rare, chronic sleep disorder characterised by excessive daytime sleepiness (EDS), unrefreshing sleep, long sleep, and sleep inertia that affects approximately 10.3 per 100,000 people[1-3]
- Currently, the only approved treatment for IH in the US are immediate-release (IR) mixed-salt oxybates, most commonly administered twice nightly (bedtime and 2.5-4 h later), which may be challenging for patients with IH with sleep inertia[4-7]
- Extended-release, once-nightly sodium oxybate (ER-OXB; LUMRYZ®) has demonstrated efficacy and safety in patients with narcolepsy and is approved in the US for the treatment of EDS or cataplexy in patients 7 years of age and older with narcolepsy[8,9]
  - The pharmacokinetic profile of ER-OXB provides drug coverage over the entire sleep period with a single, full dose at bedtime[8,9]

OBJECTIVE

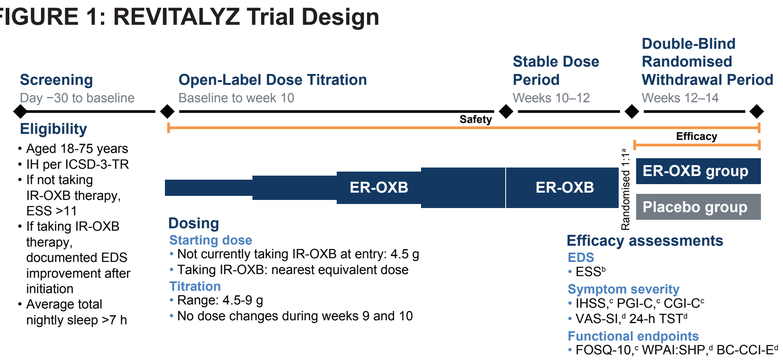
- To assess the efficacy and safety of ER-OXB for the treatment of IH in the phase 3 REVITALYZ℠ trial (NCT06525077)

METHODS

STUDY DESIGN

- REVITALYZ was a multicentre, double-blind, randomised withdrawal (DBRW) trial (**Figure 1**)
- ER-OXB dose was titrated (4.5-9 g) over a 10-week open-label dose titration (OLDT) period, followed by a 2-week stable dose period; participants were then randomised 1:1 to continue ER-OXB or switch to placebo for a 2-week DBRW period

FIGURE 1: REVITALYZ Trial Design



[a]Stratified by participants' prior use of IR-OXB therapy documented at study entry. [b]Primary endpoint. [c]Secondary endpoint. [d]Exploratory endpoint.
BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; CGI-C, Clinician Global Impression of Change; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ER-OXB, extended-release oxybate; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; ICSD-3-TR, International Classification of Sleep Disorders – Third Edition, Text Revision; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale; IR-OXB, immediate-release oxybate; PGI-C, Patient Global Impression of Change; TST, total sleep time; VAS-SI, visual analogue scale for sleep inertia; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

KEY INCLUSION CRITERIA

- Adults with a diagnosis of IH and average total nightly sleep >7 hours were eligible (**Figure 1**)
  - Participants not taking IR oxybate (IR-OXB) at study entry were required to have an Epworth Sleepiness Scale (ESS) score >11
  - Participants taking IR-OXB at study entry were required to have documented clinical improvement in EDS after IR-OXB initiation
  - Concomitant stimulants/alerting agents were permitted if the dose and regimen were stable for ≥2 months before screening

ENDPOINTS

- Primary endpoint: ESS score
- Key secondary endpoints: Patient Global Impression of Change (PGI-C) and Idiopathic Hypersomnia Severity Scale (IHSS) total score
  - Other secondary endpoints: Clinical Global Impression of Change (CGI-C) and Functional Outcomes of Sleep Questionnaire (FOSQ-10)
- Exploratory endpoints: daily visual analogue scale (VAS) for sleep inertia ("How difficult was it for you to wake up today?"; 0="very easy"; 100="very difficult"), 24-hour total sleep time (TST), Work Productivity and Activity Impairment due to IH (Specific Health Problem; WPAI:SHP), and British Columbia Cognitive Complaints Inventory-Expanded (BC-CCI-E)
- Safety and tolerability: incidence of treatment-emergent adverse events (TEAEs) throughout the study; adverse drug reactions (ADRs) were adverse events or serious adverse events deemed possibly related or related to investigational product

STATISTICAL ANALYSES

- Unless otherwise indicated, analyses were based on the intent-to-treat (ITT) population; analysis of covariance was used to assess worsening of ESS, IHSS, FOSQ-10, and exploratory endpoints from the end of the stable dose period to the end of the DBRW period in the placebo group vs the ER-OXB group
- PGI-C and CGI-C were compared using logistic regression and the Cochran–Mantel–Haenszel test, respectively, stratified by baseline IR-OXB use
- Multiplicity was controlled for the primary and all secondary endpoints using a hierarchical testing strategy; the *P* values for exploratory endpoints (ie, VAS-SI, WPAI:SHP, BC-CCI-E, and 24-hour TST) were not adjusted for multiplicity and were considered nominal
- All safety analyses were descriptive and no formal statistical testing was performed

RESULTS

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

- A total of 157 participants were enrolled and were treated in the open-label titration period (safety population)
- In the overall safety population, 59% and 41% of participants had concomitant use of stimulants and antidepressants, respectively
- 104 participants were randomised into the DBRW period and received ≥1 dose of study drug (ER-OXB, n=51; placebo, n=53 [ITT population])
- Demographic and clinical characteristics were generally balanced between ER-OXB and placebo treatment groups (**Table 1**)

TABLE 1: Demographics and Clinical Characteristics

Parameter	Baseline overall[a,b] (N=157)	Randomised population at DBRW period entry[c]	
		ER-OXB group (n=51)	Placebo group (n=53)
Age, median (range), years	39 (19-75)	39 (19-75)	39 (19-64)
Female, %	83	80	87
Race, %			
Asian	1	2	0
Black/African American	13	18	15
White	85	80	85
BMI, median (range), kg/m²	26.3 (17.7-48.5)	25.8 (17.7-48.5)	28.4 (18.9-44.6)
OXB use at study entry, %			
OXB naive	65	69	60
Switch from IR-OXB	26	26	26
Prior IR-OXB experience	9	6	13
Years since IH diagnosis, median (range)	2.3 (0-43.8)	2.6 (0-17.9)	2.7 (0.1-20.2)

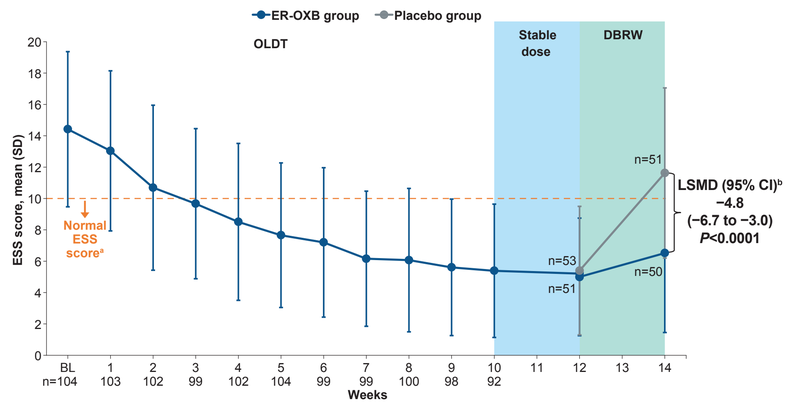
Percentages may not sum to 100% due to rounding.
[a]Safety population. [b]N=155 for IHSS at baseline. [c]Intent-to-treat population.
BMI, body mass index; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; IH, idiopathic hypersomnia; IR-OXB, immediate-release oxybate; OXB, oxybate.

EFFICACY

ESS

- The ER-OXB group had significant improvements on the ESS vs the placebo group over the DBRW period (greater worsening of EDS in the placebo group vs continued ER-OXB from the end of the stable dose period to the end of DBRW; *P*<0.0001; **Figure 2**)
- At the beginning of the OLDT period, overall mean (SD) ESS score was 14.4 (5.0)
- By week 3 of the OLDT period, mean ESS score was within the normal range (≤10)
- At the end of the stable dose period, mean (SD) ESS scores were 5.0 (3.8) and 5.4 (4.1) among participants subsequently randomised to continue ER-OXB and switch to placebo, respectively
- At the end of the DBRW period, mean (SD) ESS scores for the ER-OXB and placebo groups were 6.5 (5.1) and 11.6 (5.4), respectively
- In prespecified subgroup analyses, results were consistent and statistically significant in all groups assessed: sex (female), *P*<0.0001; age (18-64 years), *P*<0.0001; and OXB use at study entry (yes), *P*<0.0001; (no), *P*=0.0002

FIGURE 2: ESS Scores Over Time

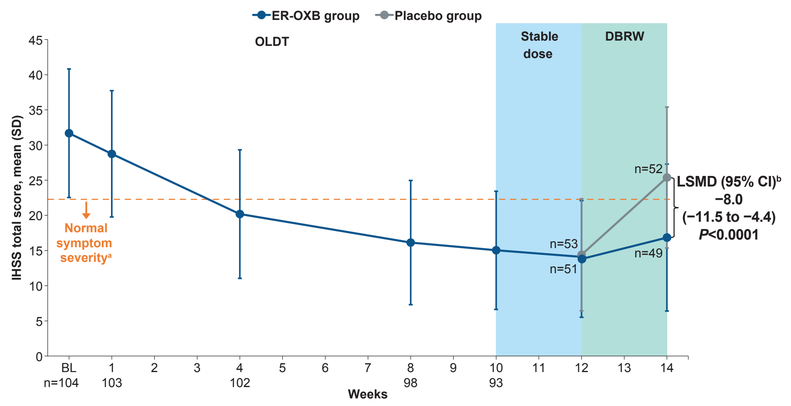


Intent-to-treat population.
[a]Normal ESS score is defined as an ESS total score ≤10.[10]
[b]LSMD (ER-OXB vs placebo) for the difference from the end of the stable dose period to the end of DBRW for each group; multiple imputation was used for the 3 participants with missing ESS scores at the end of the DBRW period.
BL, baseline; DBRW, double-blind randomised withdrawal; ESS, Epworth Sleepiness Scale; ER-OXB, extended-release oxybate; LSMD, least squares mean difference; OLDT, open-label dose titration.

IHSS

- The ER-OXB group had significant improvements on the IHSS vs the placebo group over the DBRW period (greater worsening of IHSS in the placebo group vs continued ER-OXB from the end of the stable dose period to the end of DBRW; *P*<0.0001; **Figure 3**)
- At the beginning of the OLDT period, overall mean (SD) IHSS total score was 31.7 (9.1)
- By week 4 of the OLDT period, mean IHSS score was below the threshold of normal symptom severity (≤22)
- At the end of the stable dose period, mean (SD) IHSS total scores were 13.8 (8.3) and 14.4 (8.0) among participants subsequently randomised to continue ER-OXB and switch to placebo, respectively
- At the end of the DBRW period, mean (SD) IHSS total scores for the ER-OXB and placebo groups were 16.8 (10.4) and 25.4 (10.0), respectively

FIGURE 3: IHSS Total Scores Over Time

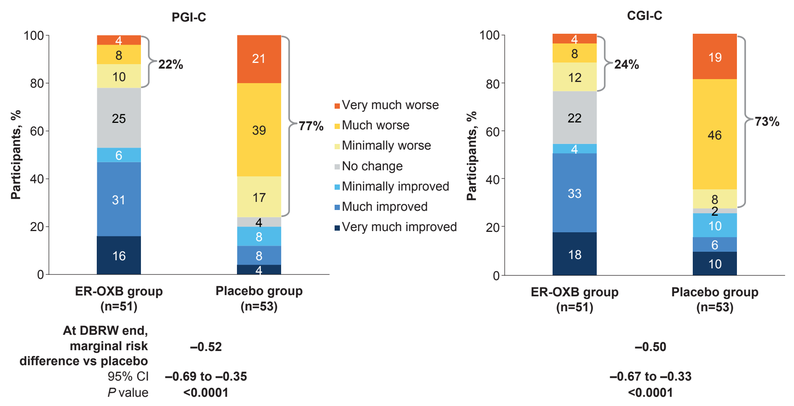


Intent-to-treat population.
[a]Normal symptom severity is defined as an IHSS total score ≤22.[11]
[b]LSMD (ER-OXB vs placebo) for the difference from the end of the stable dose period to the end of DBRW for each group; multiple imputation was used for the 3 participants with missing IHSS scores at the end of the DBRW period.
BL, baseline; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; IHSS, Idiopathic Hypersomnia Severity Scale; LSMD, least squares mean difference; OLDT, open-label dose titration.

PGI-C and CGI-C

- Withdrawal of ER-OXB led to significantly worse PGI-C and CGI-C outcomes vs continued ER-OXB over the DBRW period (**Figure 4**)

FIGURE 4: PGI-C and CGI-C at the End of the DBRW Period

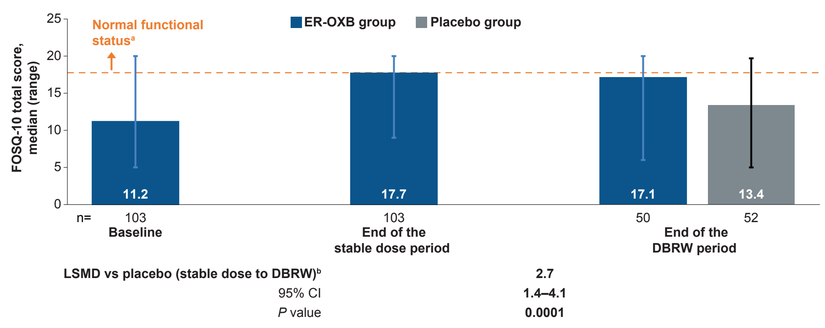


Intent-to-treat population. Percentages may not sum to 100% due to rounding. PGI-C results are from imputed values.
CGI-C, Clinical Global Impression of Change; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; PGI-C, Patient Global Impression of Change.

FOSQ-10

- Withdrawal of ER-OXB led to significantly greater worsening of FOSQ-10 total score vs continued ER-OXB over the DBRW period (*P*=0.0001; **Figure 5**)

FIGURE 5: FOSQ-10 Total Score Over Time



Intent-to-treat population.
[a]Normal functional status, 17.9-20; functional impairment, <17.9.[12]
[b]LSMD (ER-OXB vs placebo) for the difference from the end of the stable dose period to the end of DBRW for each group.
DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; LSMD, least squares mean difference.

Functional outcomes

- Withdrawal of ER-OXB led to significantly greater worsening in sleep inertia VAS scores (*P*=0.0003), most WPAI:SHP domain scores (except work time missed due to IH), BC-CCI-E total score (*P*=0.0016), and all BC-CCI-E functional impairment items vs continued ER-OXB during the 2-week DBRW period
  - WPAI:SHP domains included percent work time missed due to IH (*P*=0.4741), impairment while working due to IH (*P*<0.0001), overall work impairment due to IH (*P*=0.0003), and activity impairment due to IH (*P*<0.0001)
  - BC-CCI-E functional impairment items included difficult to do my work (*P*=<0.0001), difficult to have good relationships (*P*=0.0005), and difficult to enjoy activities (*P*<0.0001)
- Withdrawal of ER-OXB did not lead to a significant change in 24-hour TST vs continued ER-OXB during the 2-week DBRW period (*P*=0.1594)

SAFETY

- Most TEAEs were mild (38%) or moderate (34%) in severity (**Table 2**)
  - The most common TEAEs (ie, those that occurred in ≥10% of participants overall) were nausea, headache, anxiety, dizziness, and vomiting; no new safety signals were observed
- ADRs were reported by 65% of participants across all study periods, with the highest incidence at the beginning of the trial and decreasing over time
  - 1 participant experienced a serious ADR of mental status change that was related to treatment
  - ≥5% of participants experienced nausea (23%), anxiety (15%), headache (14%), dizziness (12%), vomiting (10%), enuresis (6%), tremor (6%), decreased appetite (5%), and fatigue (5%)
  - 11% of participants had an ADR leading to study discontinuation

TABLE 2: Treatment-Emergent Adverse Events (Safety Population)

Parameter	OLDT period (n=157)	Stable dose period (n=119)	DBRW period (n=104)	
			ER-OXB group (n=51)	Placebo group (n=53)
TEAE				
Any TEAE	82%	16%	22%	25%
Any serious TEAE[a]	2%	1%	0%	0%
Any TEAE leading to discontinuation	10%	3%	0%	0%

No deaths occurred.
[a]Serious TEAEs included major depression (n=1), mental status change (n=1; considered related to ER-OXB), diverticulitis (n=1), and acute myeloid leukaemia (n=1).
DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; OLDT, open-label dose titration; TEAE, treatment-emergent adverse event.

STUDY LIMITATIONS

- Only participants who tolerated ER-OXB and completed the 10-week OLDT and 2-week stable dose periods entered the DBRW period, which may represent an enriched population
- The 2-week stable dose period may not have been long enough to allow full symptom stabilisation before withdrawal; some results may be underestimated
- Modest worsening in the ER-OXB group during the DBRW period may reflect a potential nocebo effect[13]
- As this trial included both participants who were and were not taking IR-OXB at study entry, prior IR-OXB exposure may have influenced outcomes
- No separate analysis was conducted for long sleepers

CONCLUSIONS

- A single, full therapeutic dose of ER-OXB taken once at bedtime delivered statistically significant and clinically meaningful benefits in patients with IH
- REVITALYZ met the primary endpoint and secondary endpoints for EDS and symptom severity which were clinically meaningful and statistically significant
- Placebo-controlled data showed clinically relevant cognitive and functional benefits with ER-OXB
  - REVITALYZ is the first placebo-controlled trial showing significant and clinically relevant changes in BC-CCI with an OXB in IH
- ER-OXB was generally well tolerated and aligned with the known safety profile of OXBs

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DISCLOSURES

RKB has served as an adviser and/or consultant for Alkermes, Inc., Axsome Therapeutics, Daiichi Sankyo, Eisai, Jazz Pharmaceuticals, Noctrix Health, and Takeda Pharmaceutical Co.; has received industry funding for research from Apnimed, Avadel Pharmaceuticals, Bayer, BresoTec, Centessa Pharmaceuticals, Clinilabs, Eisai, FRESCA Medical, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Lilly, LivaNova, Merck & Co., NLS Pharmaceutics, Novo Nordisk, Pfizer, Philips, Roche, Samsung, Sommetrics, Suven Life Sciences Ltd., Takeda Pharmaceutical Co., and Vanda Pharmaceuticals; and has served on speakers bureaus for Axsome Therapeutics, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, and Noctrix Health. **JH** has nothing to disclose. **SI** is affiliated with a hospital that has received funding for research from Avadel Pharmaceuticals and has received research grant funding from Centessa Pharmaceuticals, Harmony Biosciences, Jazz Pharmaceuticals, Takeda Pharmaceutical Co., and the National Institutes of Health. **JCC** has received research funding from Alkermes, Inc., Avadel Pharmaceuticals, Inspire Medical Systems, Lilly, and Sommetrics and has served as a consultant and/or on advisory boards for Alkermes, Inc., Apnimed, Avadel Pharmaceuticals, Fisher & Paykel Healthcare, Inspire Medical Systems, ResMed, and Zoll Medical. **AMM** has served as an investigator, consultant, speaker, and/or on advisory boards for Alkermes, Inc., Apnimed, Avadel Pharmaceuticals, Axsome Therapeutics, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, Lilly, Lundbeck, Noble Pharmaceuticals, Novartis, and Takeda Pharmaceutical Co.; has received grant funding from Coverys Community Healthcare Foundation, Geisinger Health Plan, Harmony Biosciences, the National Institutes of Health, ResMed Foundation, and UCB Pharmaceuticals; is the Chief Executive Officer of DAMM Good Sleep, LLC; is the chairman of the clinical advisory board for NanoMosaic; and serves as an adviser for FloraWorks, Neura Health, OpenEvidence, and Pulse Infoframe. **BCC** is a member of the speakers bureaus of Eisai, Harmony Biosciences, Jazz Pharmaceuticals, and Merck & Co. He has served as an adviser for and has received consulting fees and honoraria from Avadel Pharmaceuticals. **TS** has served as a consultant and speaker for Avadel Pharmaceuticals. **EM** has received clinical trial or research funding from Apple, Avadel Pharmaceuticals, Eisai, Jazz Pharmaceuticals, Suven Life Sciences Ltd., and Takeda Pharmaceutical Co.; owns stocks in Centessa Pharmaceuticals and Sleep Apnea Co.; and has consulted for or received honorarium from Avadel Pharmaceuticals, Idorsia, Jazz Pharmaceuticals, and Takeda Pharmaceutical Co. **YD** has served as a consultant/advisory board member for Alkermes, Inc., Avadel Pharmaceuticals, Bioprojet, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Lundbeck, Centessa Pharmaceuticals, and Takeda Pharmaceutical Co. **JB**, **BA**, and **GSR** are employees of Alkermes, Inc.

REFERENCES

1. Acquavella J, et al. *J Clin Sleep Med*. 2020;16(8):1255-1263.
2. Fronczek R, et al. *Sleep*. 2020;43(8).
3. Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709.
4. Xywav® (calcium, magnesium, potassium, and sodium oxybate). Full Prescribing Information. Jazz Pharmaceuticals, Inc; 2025.
5. Yu J, et al. Real-world, participant-reported effectiveness and satisfaction with low-sodium oxybate in idiopathic hypersomnia. Presented at: SLEEP 2025; June 8-11, 2025; Seattle, WA.
6. Plante DT, et al. *CNS Drugs*. 2026.
7. Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.
8. Kushida CA, et al. *Sleep*. 2022;45(6):1-11.
9. LUMRYZ® (sodium oxybate for extended-release oral suspension, CIII). Full Prescribing Information. Alkermes, Inc.; 2026.
10. Johns MW. *Sleep*. 1991;14(6):540-545.
11. Dauvilliers Y, et al. *Neurology*. 2019;92(15):e1754-e1762.
12. Weaver TE, et al. *Sleep*. 2007;30(6):711-719.
13. Trotti LM. *Lancet Neurol*. 2022;21(1):25-26.

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