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

Richard K. Bogan, MD, FCCP, FAASM[1,2]; John Harsh, PhD[3]; Sally Ibrahim, MD[4,5]; John C. Carter, MD[5,6]; Anne Marie Morse, DO[7]; Bruce C. Corser, MD[8]; Thomas Stern, MD[9]; Jacqueline Brooks, MBBCh, MRCPsych[10]; Brian Abaluck, MD[10]; Gretchen S. Richards, MS[10]

[1]University of South Carolina School of Medicine, Columbia, SC, USA; [2]Medical University of South Carolina, Charleston, SC, USA; [3]University of Colorado, Boulder, CO, USA; [4]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [5]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [6]The MetroHealth System, Cleveland, OH, USA; [7]Geisinger Commonwealth School of Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, PA, USA; [8]Sleep Management Institute, Cincinnati, OH, USA; [9]Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA; [10]Alkermes, Inc., Waltham, MA, USA*

Poster 530

INTRODUCTION

- Idiopathic hypersomnia (IH) and narcolepsy are rare, chronic central disorders of hypersomnolence characterized by excessive daytime sleepiness (EDS)[1]
  - Patients with IH also present with sleep inertia and may experience unrefreshing or nonrestorative sleep[1,2]
  - These symptoms have a strong negative effect on patients' daily life and their psychological and emotional well-being[2]
- There remains a substantial unmet need for effective treatment options for patients with IH; in a 2024 patient-focused drug development initiative survey[3] of >800 patients with IH or their caregivers:
  - 60% of respondents reported IH symptoms were poorly controlled or not controlled at all
  - >50% reported ineffective treatment or loss of treatment effectiveness over time
  - Approximately 40% reported too many side effects or side effects that they were unwilling to tolerate
- Currently, there is only 1 US Food and Drug Administration (FDA)-approved medication for the treatment of IH (immediate-release, mixed-salt oxybates [IR mixed-salt OXBs], approved in 2021)[4]
- In clinical and real-world studies of participants with IH who took IR mixed-salt OXBs once or twice nightly (ie, at bedtime or at bedtime and 2.5-4 h later), the twice-nightly dosing regimen was more common, ranging from 63%-79% of participants[4-6]
  - Reduced efficacy of IR mixed-salt OXBs has been shown with the single dose compared to the twice-nightly dose,[7] and the twice-nightly dosing regimen may be challenging for patients with IH, particularly those who experience sleep inertia
- Extended-release sodium oxybate (ER-OXB [LUMRYZ® (sodium oxybate) for extended-release oral suspension, Avadel Pharmaceuticals]) is FDA-approved to treat EDS or cataplexy in patients 7 years of age and older with narcolepsy[8]
  - The pharmacokinetic profile of ER-OXB provides drug coverage over the entire sleep period with a single, full dose at bedtime[8]
  - ER-OXB has been recognized by the FDA as a major contribution to narcolepsy patient care owing to the omission of the middle-of-the-night dose required by IR OXBs[9]

OBJECTIVE

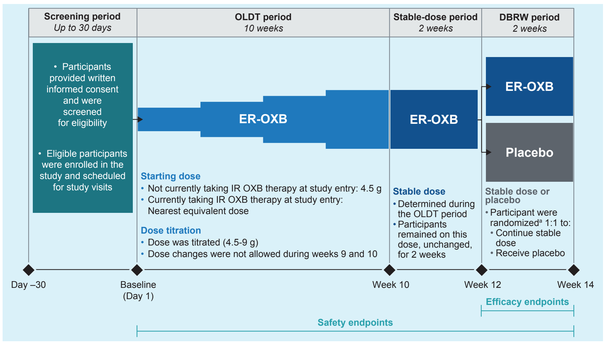
- To describe the design, patient cohort, and topline efficacy and safety results of ER-OXB for treatment of IH in the phase 3 REVITALYZ℠ trial (NCT06525077)[10]

METHODS

STUDY DESIGN

- REVITALYZ was a 14-week, multicenter, double-blind, randomized withdrawal (DBRW) trial of ER-OXB in participants with IH in the United States (**Figure 1**)
  - ER-OXB was titrated over a 10-week period (dose range, 4.5-9.0 g), followed by a 2-week stable-dose period
  - In the subsequent 2-week DBRW period, participants were randomized 1:1 to continue ER-OXB or switch to placebo

FIGURE 1: REVITALYZ Trial Design



DBRW, double-blind randomized withdrawal; ER-OXB, extended-release sodium oxybate; IR, immediate-release; OLDT, open-label dose titration; OXB, oxybate.
[a]Stratified by participants' prior use of IR OXB therapy documented at study entry.

PARTICIPANTS

- Participants aged 18-75 years with a primary diagnosis of IH were eligible, regardless of current or prior IR OXB use (**Figure 2**)
- Concomitant stimulant or alerting agent use was permitted if:
  - Dose and regimen were stable for ≥2 months prior to screening
  - The same dose and regimen were maintained leading up to and throughout the DBRW period

FIGURE 2: Key Inclusion and Exclusion Criteria

Key inclusion criteria

- Aged 18-75 years
- Primary diagnosis of IH according to the ICSD-3-TR criteria
- If not taking IR OXB therapy, ESS total score >11
- If taking IR OXB therapy, documented clinical improvement of EDS after IR OXB initiation
- Average total nightly sleep >7 h per participant history and confirmed by the screening period sleep diary

Key exclusion criteria

- Prior treatment with ER-OXB
- Current or past substance use disorder according to DSM-5 criteria
- History or presence of seizures, excluding childhood benign febrile seizures
- History or presence of certain mental health disorders, including ongoing or past (≤1 y) major depressive episode, according to DSM -5 criteria
- Hypersomnia due to another medical, behavioral, sleep, or psychiatric condition
- Untreated or incompletely treated moderate -severe sleep apnea in participants with apnea-hypopnea index ≥15
- Clinically significant parasomnias as determined by the investigator's clinical judgment

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EDS, excessive daytime sleepiness; ER-OXB, extended-release sodium oxybate; ESS, Epworth Sleepiness Scale; ICSD-3-TR, *International Classification of Sleep Disorders–Third Edition, Text Revision*; IH, idiopathic hypersomnia; IR, immediate-release; OXB, oxybate.

ENDPOINTS AND CLINICAL ASSESSMENTS

- Primary endpoint: change in Epworth Sleepiness Scale (ESS) score from the end of the stable-dose period to the end of the DBRW period (**Figure 3**)
- Key secondary endpoints: worsening of IH symptoms on the Patient Global Impression of Change (PGI-C) and changes in IH symptom severity on the Idiopathic Hypersomnia Severity Scale (IHSS)
- Safety and tolerability were assessed throughout the 14-week study

FIGURE 3: Primary, Key Secondary, and Safety Endpoints

Endpoint	Domain	Assessment	Outcome measure	Time period
Primary endpoint	EDS	Change in ESS total score	Worsening of ESS total score in the placebo group vs ER-OXB group	2 weeks: End of stable-dose period – End of DBRW period
Key Secondary endpoints	Symptom severity	Change in disease-specific symptoms as assessed by PGI-C	Worsening of IH symptoms as assessed by PGI-C in the placebo group vs ER-OXB group	2 weeks: End of stable-dose period – End of DBRW period
		Change in IHSS total score	Worsening of IHSS total score in the placebo group vs ER-OXB group	
Safety and tolerability	Safety	Incidence of adverse events	Summary of adverse event incidence in the placebo and ER-OXB groups	14 weeks: Start of OLDT period – End of DBRW period

DBRW, double-blind randomized withdrawal; EDS, excessive daytime sleepiness; ER-OXB, extended-release sodium oxybate; ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale; OLDT, open-label dose titration; PGI-C, Patient Global Impression of Change.

ANALYSES

- Efficacy analyses were assessed in all participants who were randomized and received ≥1 dose of ER-OXB or placebo during the DBRW period
  - ESS total score and IHSS total score were assessed by analysis of covariance with fixed effects for treatment group, prior IR OXB experience at study entry, and baseline score at the end of the stable-dose period
  - PGI-C was assessed by logistic regression adjusted by prior IR OXB experience at study entry
- The safety population included all participants who received ≥1 dose of ER-OXB
- Additional findings of the REVITALYZ study will be reported in future presentations

RESULTS

BASELINE DEMOGRAPHICS AND CHARACTERISTICS

- A total of 157 participants were enrolled in REVITALYZ
- Mean age was 39.8 years and the majority of participants were female (83%; n=130; **Table**)

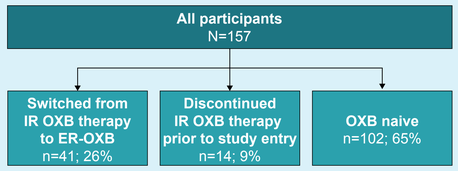
TABLE: Baseline Demographics and Clinical Characteristics (Safety Population)

Characteristic	Overall (N=157)
Age, y	
Mean (SD)	39.8 (12.9)
Median (range)	30.9 (19.0-75.0)
Sex, n (%)	
Female	130 (83)
Male	27 (17)
Race, n (%)	
Asian	2 (1)
Black/African American	21 (13)
White	134 (85)
Ethnicity, n (%)	
Hispanic or Latino	15 (10)
Not Hispanic or Latino	142 (90)
BMI, kg/m²	
Mean (SD)	27.9 (6.4)
Median (range)	26.3 (17.7-48.5)
Mean (SD) duration with an IH diagnosis, y[a]	4.7 (6.5)
Mean (SD) ESS total score[b,c]	14.3 (4.7)
Mean (SD) IHSS total score[b,d]	31.7 (9.2)

BMI, body mass index; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale.
[a]n=156. [b]n=155. [c]Normal, mild, moderate, and severe EDS defined as ESS total score of ≤10, 11-12, 13-15, and ≥16, respectively.[11,12] [d]Mild, moderate, severe, and very severe defined as IHSS total score of ≤12, 13-25, 26-38, and 39, respectively.[13]

- At study entry, 41 (26%) participants were taking IR OXB therapy (**Figure 4**)
  - Among the 116 participants not taking IR OXB therapy at study entry, 14 (12%) had previously received IR OXB therapy

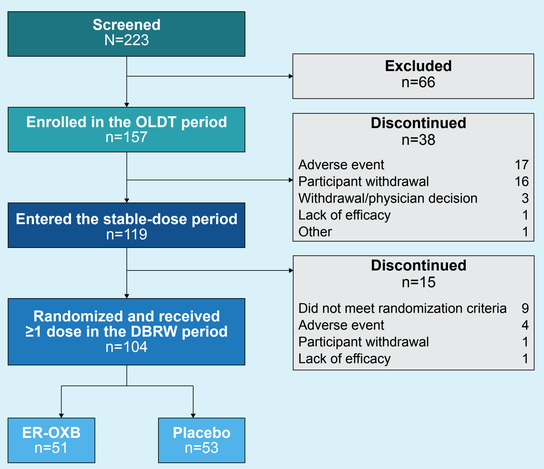
FIGURE 4: Prior IR OXB Experience at Baseline (Safety Population)



Percentages were calculated based on the total number of participants.
ER-OXB, extended-release sodium oxybate; IR, immediate-release; OXB, oxybate.

- At the end of the stable-dose period, 104 participants were randomized 1:1 to continue ER-OXB or switch to placebo for the 2-week DBRW period (**Figure 5**)

FIGURE 5: Participant Disposition



DBRW, double-blind randomized withdrawal; ER-OXB, extended-release sodium oxybate; OLDT, open-label dose titration.

SAFETY

- The most common treatment-emergent adverse events (≥10% of participants) were nausea, headache, anxiety, dizziness, and vomiting

EFFICACY

- The primary and key secondary endpoints were met; compared with participants who continued ER-OXB during the DBRW period, those randomized to placebo had statistically significant worsening in the primary endpoint of ESS total score and key secondary endpoints of PGI-C rating and IHSS total score (**Figure 6**)

FIGURE 6: Change From the End of the Stable-Dose Period to the End of the DBRW Period

Endpoint	Assessment	Worsening in the placebo group vs ER-OXB group	Endpoint met
Primary endpoint	ESS total score	*P*<0.0001	✓
Key secondary endpoints	PGI-C rating	*P*<0.0001	✓
	IHSS total score	*P*<0.0001	✓

Green check marks indicate that the endpoint was met. DBRW, double-blind randomized withdrawal; ER-OXB, extended-release sodium oxybate; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; PGI-C, Patient Global Impression of Change.

STUDY LIMITATIONS

- The DBRW period in REVITALYZ was limited to 2 weeks; however, this duration helped minimize participant burden for those not receiving the active treatment
- Given that only participants who tolerated ER-OXB and completed the 10-week stable-dose period were randomized, the data set may represent an enriched population
- Rapid symptom recurrence following randomization to placebo may reflect withdrawal or rebound effects rather than true relapse of IH-related symptoms[14]

CONCLUSIONS

- ER-OXB demonstrated statistically significant efficacy in adults with IH symptoms on the primary endpoint of ESS total score and the key secondary endpoints of PGI-C rating and IHSS total score
- ER-OXB was generally well tolerated
  - The safety profile of ER-OXB was generally consistent with previously observed safety data of ER-OXB [8,15-17]; no new safety signals were observed
- The REVITALYZ study demonstrated that an extended-release oxybate formulation can provide clinically meaningful benefits to patients with IH using a single, full therapeutic dose take once nightly

FUNDING

This study was funded by Avadel Pharmaceuticals (Chesterfield, MO). *Avadel Pharmaceuticals Limited (formerly Avadel Pharmaceuticals plc) is an affiliate of Alkermes plc. REVITALYZ℠ is a service mark and LUMRYZ® is a registered trademark of Flamel Ireland Limited, an affiliate of Alkermes plc.

REFERENCES

1. Biscarini F, et al. *J Sleep Res*. 2025:e70118.
2. Bermingham SL, et al. *PLoS One*. 2025;20(10):e0333497.
3. McCleary KK, Kith Collective. *Illuminate hypersomnia: voice of the patient report from the externally-led patient-focused drug development meeting on idiopathic hypersomnia (IH)*. Sleep Consortium; 2024.
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. Effectiveness and safety of low-sodium oxybate in idiopathic hypersomnia participants: results from the DUET study. Presented at: SLEEP 2025; June 8-11, 2025; Seattle, WA.
7. Dauvilliers Y, et al. *Lancet Neurol*. 2022;21(1):53-65.
8. LUMRYZ® (sodium oxybate for extended-release oral suspension, CIII). Full Prescribing Information. Avadel Pharmaceuticals; 2025.
9. US Food and Drug Administration. Clinical superiority findings. 2024. Accessed February 23, 2026. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings
10. ClinicalTrials.gov. Safety and efficacy of FT218 in idiopathic hypersomnia (REVITALYZ). 2026. Accessed March 1, 2026. https://clinicaltrials.gov/study/NCT06525077
11. Johns MW. About the ESS. Accessed March 5, 2026. https://epworthsleepinessscale.com/about-the-ess/
12. Johns MW. *Sleep*. 1991;14(6):540-545.
13. Rassu AL, et al. *J Clin Sleep Med*. 2022;18(2):617-629.
14. Trotti LM. *Lancet Neurol*. 2022;21(1):25-26.
15. Seiden D, et al. *Sleep*. 2020;43(suppl 1):A282-A283.
16. Kushida CA, et al. *Sleep*. 2022;45(6):1-11.
17. Roy A, et al. *Sleep Med X*. 2024;8:1-7.

Acknowledgments, disclosure information, and copies of this poster can be obtained through this QR (Quick Response) code

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

Richard K. Bogan, MD, FCCP, FAASM[1,2]; John Harsh, PhD[3]; Sally Ibrahim, MD[4,5]; John C. Carter, MD[5,6]; Anne Marie Morse, DO[7]; Bruce C. Corser, MD[8]; Thomas Stern, MD[9]; Jacqueline Brooks, MBBCh, MRCPsych[10]; Brian Abaluck, MD[10]; Gretchen S. Richards, MS[10]

[1]University of South Carolina School of Medicine, Columbia, SC, USA; [2]Medical University of South Carolina, Charleston, SC, USA; [3]University of Colorado, Boulder, CO, USA; [4]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [5]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [6]The MetroHealth System, Cleveland, OH, USA; [7]Geisinger Commonwealth School of Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, PA, USA; [8]Sleep Management Institute, Cincinnati, OH, USA; [9]Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA; [10]Alkermes, Inc., Waltham, MA, USA*

Poster 530

ACKNOWLEDGMENTS

Medical writing support was provided by Kelby Killoy, PhD, from Citrus Health Group, Inc. (Chicago, IL), and was funded by Avadel Pharmaceuticals (Chesterfield, MO).

DISCLOSURES

RKB has served as an advisor 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, and the National Institutes of Health.

JCC has received research funding from Avadel Pharmaceuticals, Inspire Medical, and Sommetrics and has served as a consultant and/or on advisory boards for 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, Noble Pharmaceuticals, Novartis, and Takeda Pharmaceutical Co.; has received grant funding from Coverys Community Healthcare Foundation, Geisinger Health Plan, Harmony Biosciences, Jazz Pharmaceuticals, the National Institutes of Health, ResMed Foundation, and UCB Pharmaceuticals; is the Chief Executive Officer of DAMM Good Sleep, LLC; and serves as an advisor for FloraWorks, Neura Health, and OpenEvidence.

BCC is a member of the speakers' bureaus of Eisai, Harmony Biosciences, Jazz Pharmaceuticals, and Merck & Co. He has served as an advisor for and has received consulting fees and honoraria from Avadel Pharmaceuticals.

TS has served as a consultant and speaker for Avadel Pharmaceuticals.

JB, **BA**, and **GSR** are employees of Alkermes, Inc.