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REVITALYZ

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

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Disclosures and Study Support

I declare the following potential conflicts of interest:

Richard K. Bogan 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.

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Idiopathic Hypersomnia: Diagnosis and Burden

Rare, chronic sleep disorder with EDS, unrefreshing sleep, long sleep time, and sleep inertia[1,2]

IH diagnosis requires[3]:

- EDS ≥3 months
- No cataplexy
- No orexin deficiency
- MSLT or PSG not consistent with a narcolepsy diagnosis

IH is associated with multiple comorbidities, including sleep, metabolic, and psychiatric/mood disorders[4,5]

Patients with IH may experience challenges with work/school, mental health, activities of daily living, and engaging with others socially[6]

EDS, excessive daytime sleepiness; IH, idiopathic hypersomnia; MSLT, Multiple Sleep Latency Test; PSG, polysomnography.

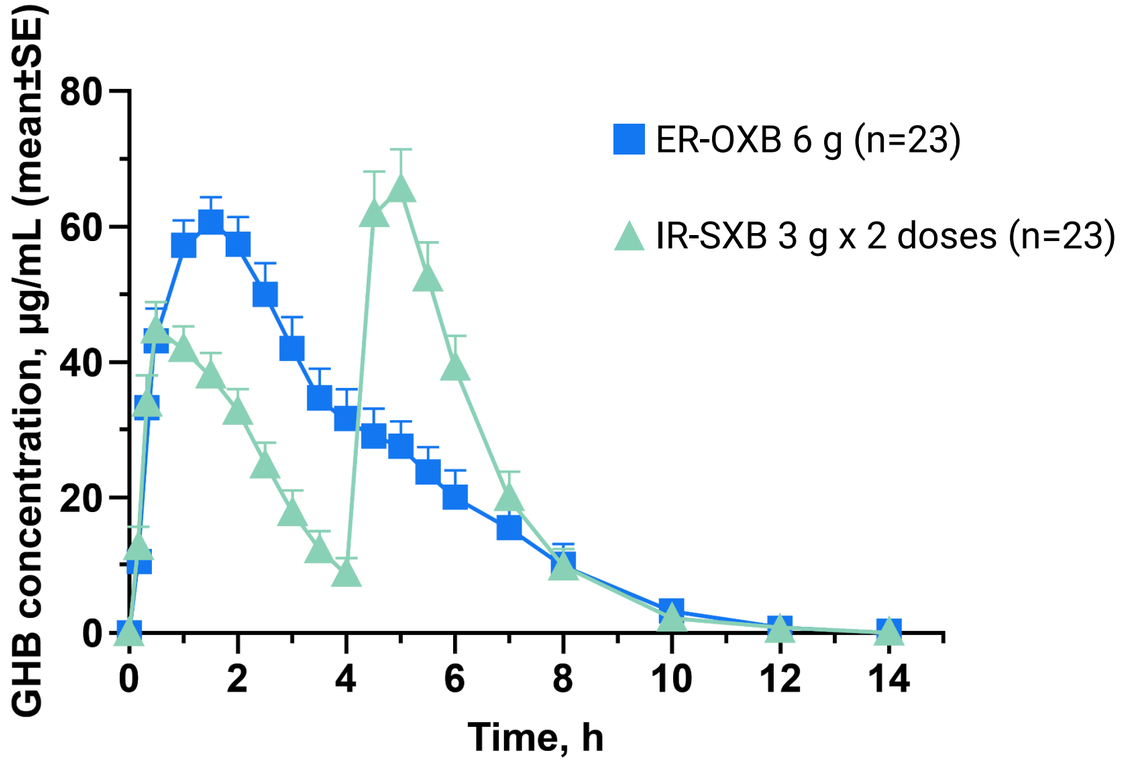
1. Biscarini F, et al. *J Sleep Res*. 2025:e70118. 2. Bermingham SL, et al. *PLoS One*. 2025;20(10):e0333497. 3. American Academy of Sleep Medicine. ICSD-3-TR. 2023. 4. Lillaney P, et al. *Sleep*. 2023;46:A373. 5. Saad R, et al. *Sleep Epidemiology*. 2023;3:100059. 6. Williams W, et al. *Sleep*. 2025;48(supplement 1):A368.

Single Bedtime Dose of ER-OXB Provides Drug Coverage Over the Entire Sleep Period

Clinical Context

- In the US, the IR mixed-salt oxybate formulation is approved for IH
  - IR oxybate is most commonly taken twice nightly (eg, bedtime and 2.5-4 h later)[1-3]
- Efficacy and safety of a single bedtime dose of ER-OXB have been demonstrated for the treatment of narcolepsy symptoms[4-7]
- The REVITALYZ℠ trial investigated ER-OXB for the treatment of IH

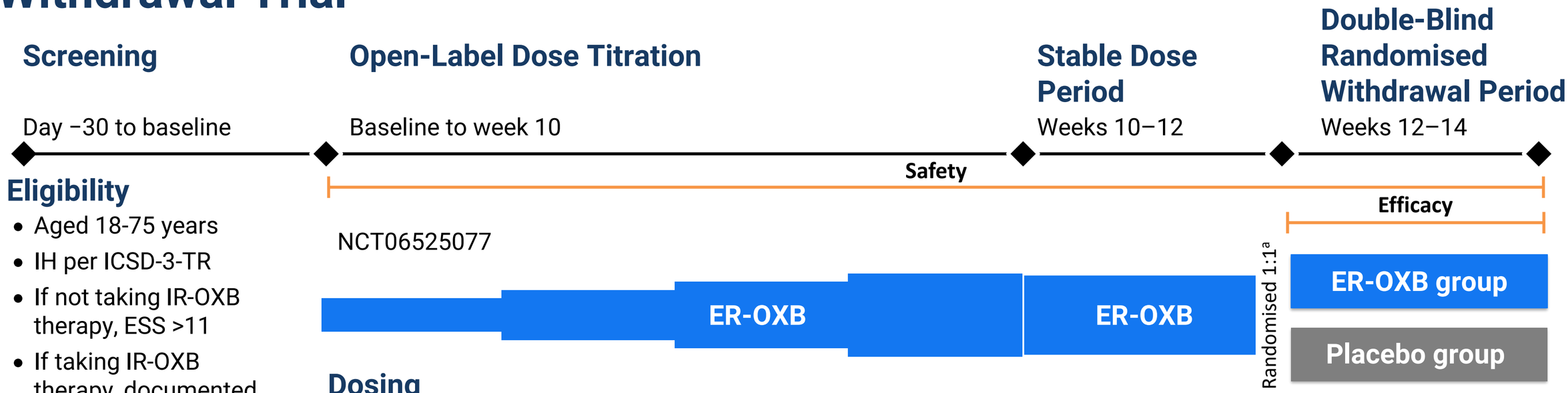
A Single ER-OXB Dose is Bioequivalent to 2 IR-SXB Doses[8]



ER-OXB, extended-release oxybate; GHB, γ-hydroxybutyrate; IH, idiopathic hypersomnia; IR-SXB, immediate-release sodium oxybate.

1. Xywav®. Full prescribing information. 2025. 2. Yu J, et al. Real-world, participant-reported effectiveness and satisfaction with low-sodium oxybate in idiopathic hypersomnia. SLEEP 2025; June 8-11, 2025; Seattle, WA. 3. Plante DT, et al. *CNS Drugs*. 2026 Jun;40(6):803-822. 4. Kushida CA, et al. *Sleep*. 2022;45(6):1-11. 5. Roth T, et al. *CNS Drugs*. 2022;36(4):377-387. 6. Roy A, et al. *Sleep Med X*. 2024;8:1-7. 7. LUMRYZ®. Full prescribing information. 2026. 8. Bogan R, et al. *Sleep Med*. 2022;100:442-447.

REVITALYZ: Phase 3, Double-Blind, Placebo-Controlled, Randomised Withdrawal Trial



Eligibility

- Aged 18-75 years
- IH per ICSD-3-TR
- If not taking IR-OXB therapy, ESS >11
- If taking IR-OXB therapy, documented EDS improvement after initiation
- Average total nightly sleep >7 h

Dosing

Starting dose

- Not currently taking IR-OXB at entry: 4.5 g
- Taking IR-OXB: nearest equivalent dose

Titration

- Range: 4.5-9 g
- No dose changes during weeks 9 and 10

Efficacy assessments

EDS

- ESS[b]

Symptom severity

- IHSS,[c] PGI-C,[c] CGI-C[d]
- VAS-SI,[e] 24-h TST[e]

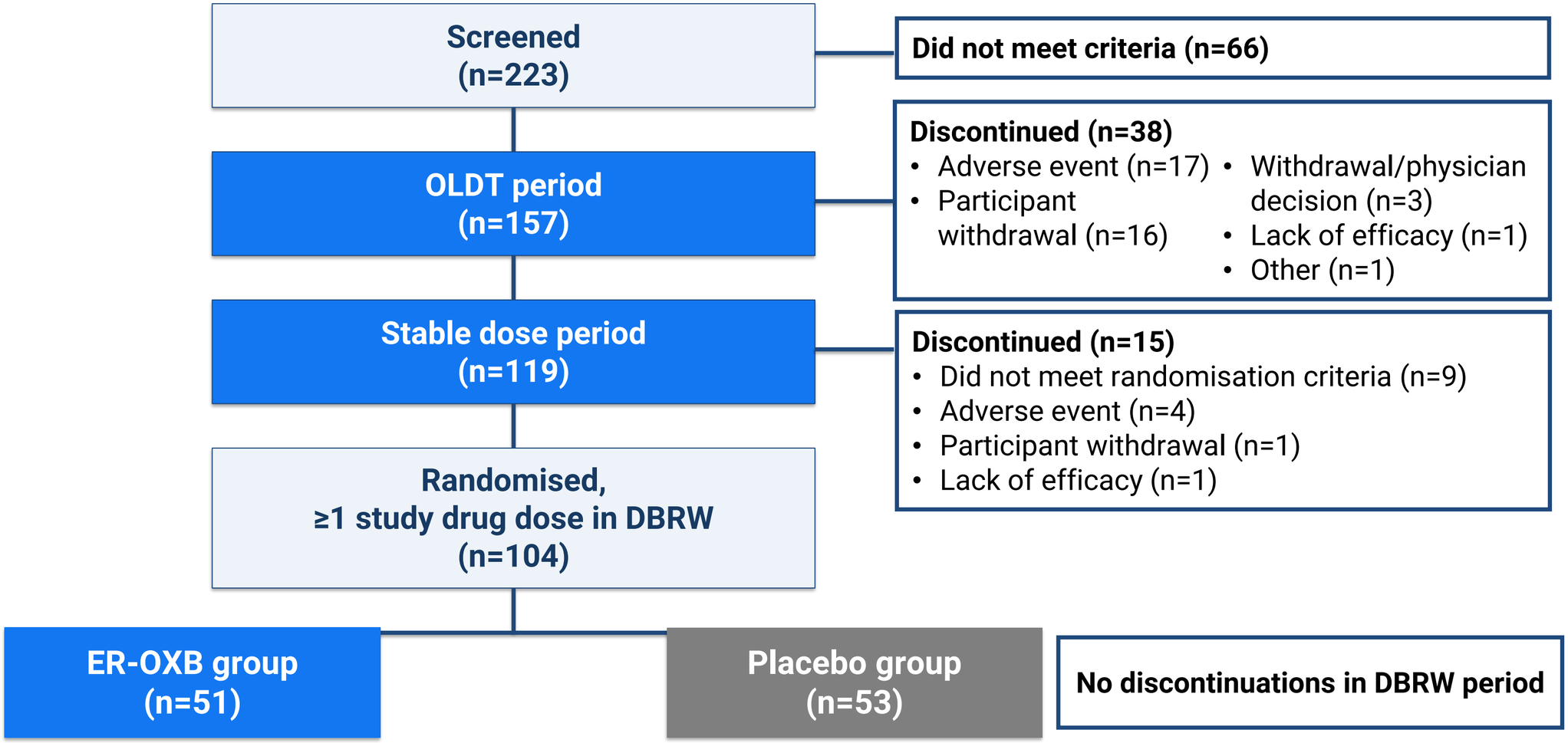
Functional endpoints

- FOSQ-10,[d] WPAI:SHP,[e] BC-CCI-E[e]

NCT06525077

[a]Stratified by participants' prior IR-OXB use documented at study entry. [b]Primary endpoint. [c]Key secondary endpoint. [d]Secondary endpoint. [e]Exploratory endpoint.
BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; CGI-C, Clinical Global Impression of Change; EDS, excessive daytime sleepiness; ER-OXB, extended-release oxybate; ESS, Epworth Sleepiness Scale; 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.

Participant Disposition



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

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Baseline Demographics and Clinical Characteristics

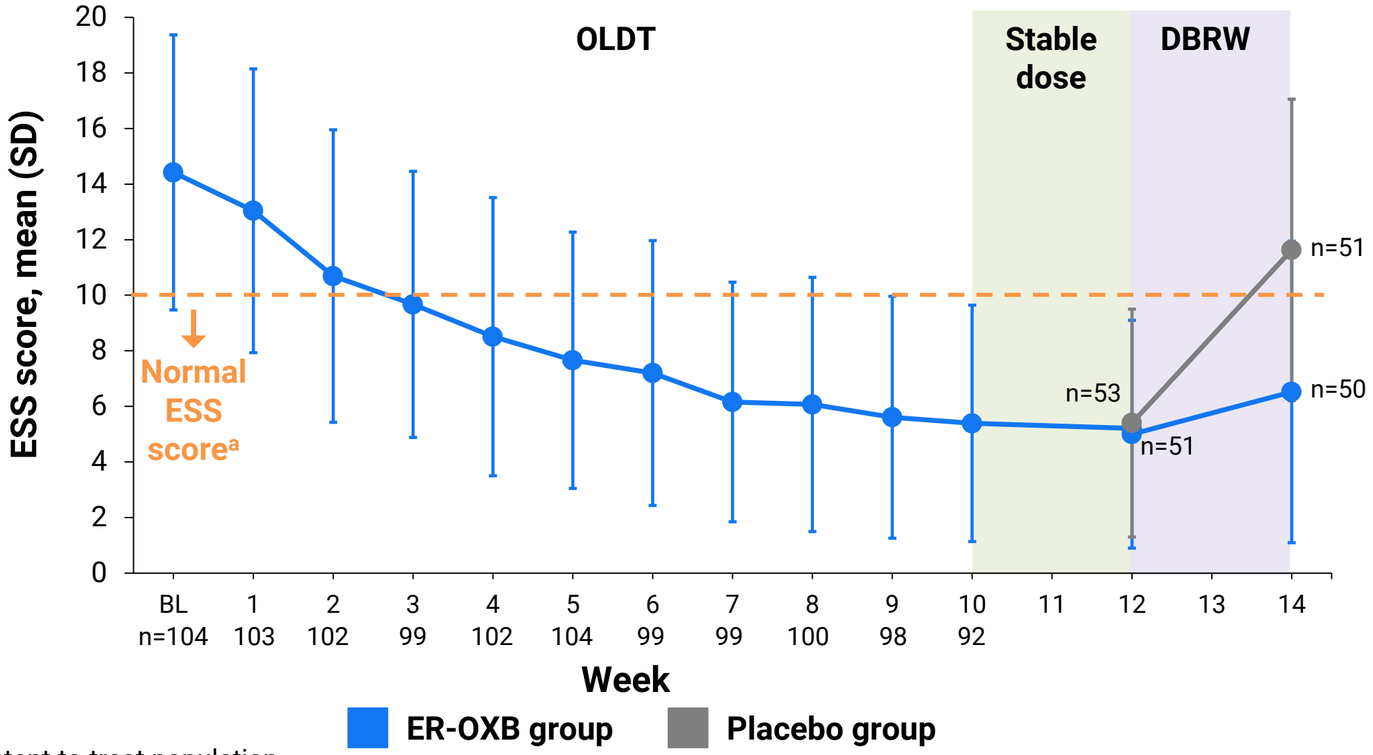
Parameter	Baseline overall[a] (N=157)	Randomised population at DBRW period entry[b] (n=104)	
		ER-OXB group (n=51)	Placebo group (n=53)
Age, median (range), years	39 (19-75)	39 (19-75)	39 (19-64)
Female, %	83	80	87
Race, %			
Asian	1	2	0
Black/African American	13	18	15
White	85	80	85
BMI, median (range), kg/m^2	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 (0.0-43.8)	2.6 (0.0-17.9)	2.7 (0.1-20.2)

Percentages may not sum to 100% due to rounding.
[a]Safety population=all participants who received ≥1 dose of study drug.
[b]Intent-to-treat population=all randomised participants who received ≥1 dose of study drug during the double-blind randomised withdrawal period.
BMI, body mass index; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; IH, idiopathic hypersomnia; IR-OXB, immediate-release oxybate; OXB, oxybate.

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Improvement on ESS Maintained with ER-OXB vs Placebo

Primary endpoint: Worsening of EDS from end of the stable dose period to end of the DBRW period vs continued ER-OXB



ESS score[a]		ER-OXB group	Placebo group
End of stable dose	Participants, n	51	53
	Mean (SD)	5.0 (3.8)	5.4 (4.1)
End of DBRW	Participants, n	50	51
	Mean (SD)	6.5 (5.1)	11.6 (5.4)
	LSMD (95% CI) vs placebo (stable dose to DBRW)[b]	**−4.8 (−6.7 to −3.0) *P*<0.0001**	

Intent-to-treat population.

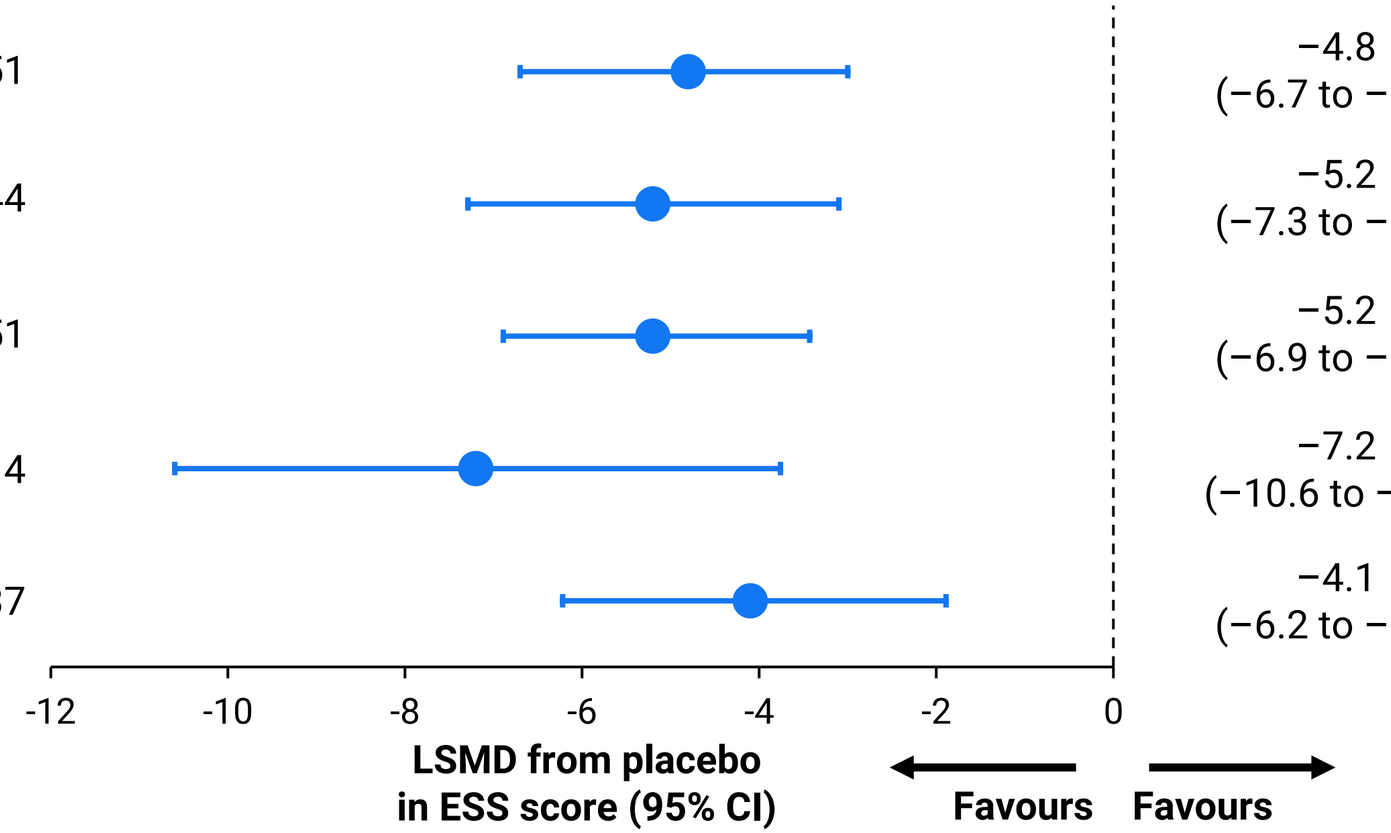
[a]Normal ESS score is defined as an ESS total score ≤10.(Johns MW. *Sleep*. 1991;14(6):540-545).

[b]LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group; multiple imputation was used for 3 participants with missing ESS scores at the end of the DBRW period.

BL, baseline; DBRW, double-blind randomised withdrawal; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ER-OXB, extended-release oxybate; LSMD, least squares mean difference; OLDT, open-label dose titration.

ESS Response Consistently Favoured ER-OXB Group Across Subgroups

	ER-OXB group (n=51)	Placebo group (n=53)	LSMD from placebo in ESS score (95% CI)	*P* value
Overall	50	51	−4.8 (−6.7 to −3.0)	<0.0001
Sex, female	40	44	−5.2 (−7.3 to −3.1)	<0.0001
Age, 18–64 y	47	51	−5.2 (−6.9 to −3.4)	<0.0001
Oxybate use at study entry				
Yes	12	14	−7.2 (−10.6 to −3.8)	<0.0001
No	38	37	−4.1 (−6.2 to −1.9)	0.0002

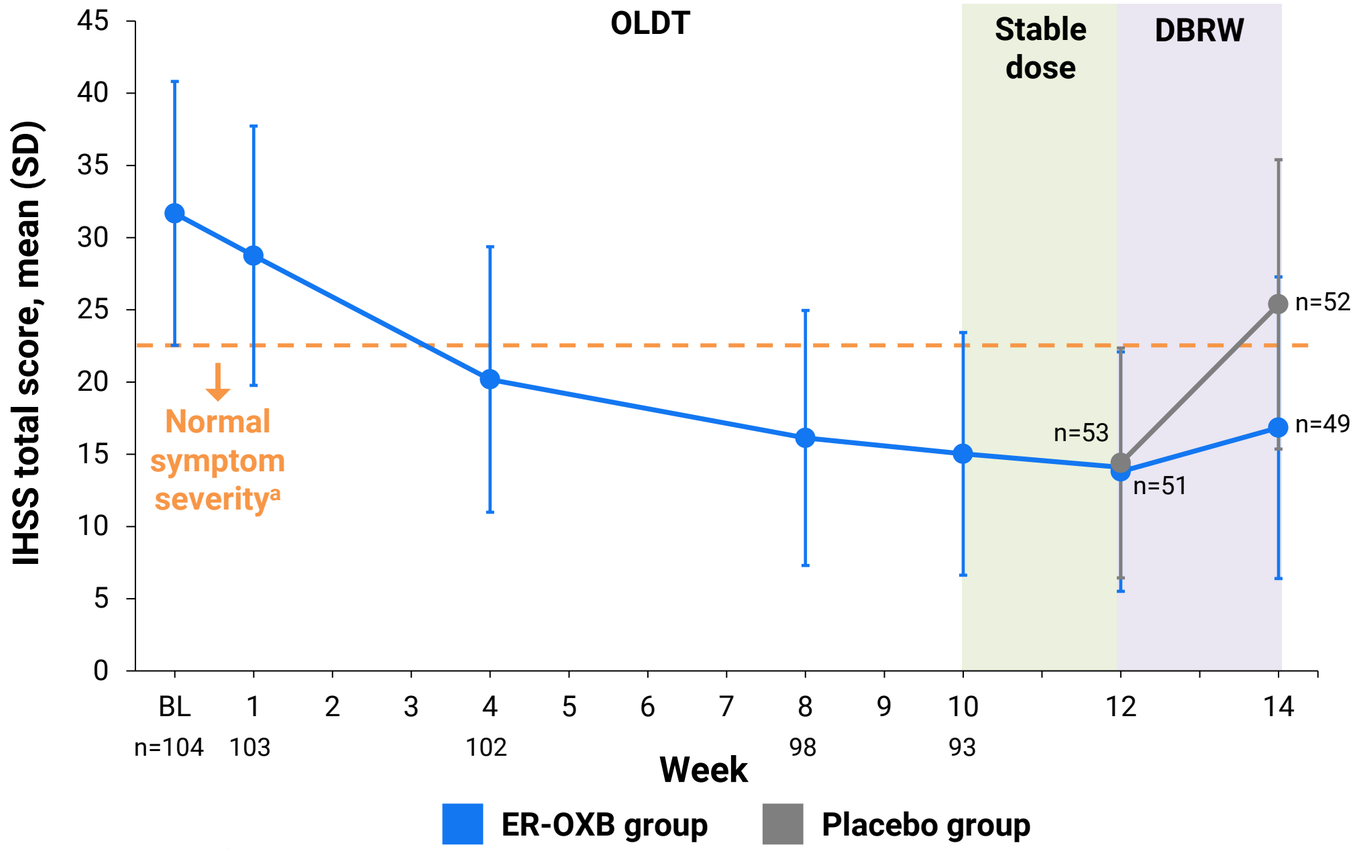


Intent-to-treat population.
Subgroups were pre-specified.
LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group.
DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; ESS, Epworth Sleepiness Scale; LSMD, least squares mean difference.

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Improvement on the IHSS Maintained with ER-OXB vs Placebo

Secondary endpoint: Worsening of IHSS from end of the stable dose period to end of the DBRW period vs continued ER-OXB



IHSS total score[a]		ER-OXB group	Placebo group
End of stable dose	Participants, n	51	53
	Mean (SD)	13.8 (8.3)	14.4 (8.0)
End of DBRW	Participants, n	49	52
	Mean (SD)	16.8 (10.4)	25.4 (10.0)
	LSMD (95% CI) vs placebo (stable dose to DBRW)[b]	**−8.0 (−11.5 to −4.4) *P*<0.0001**	

Intent-to-treat population.

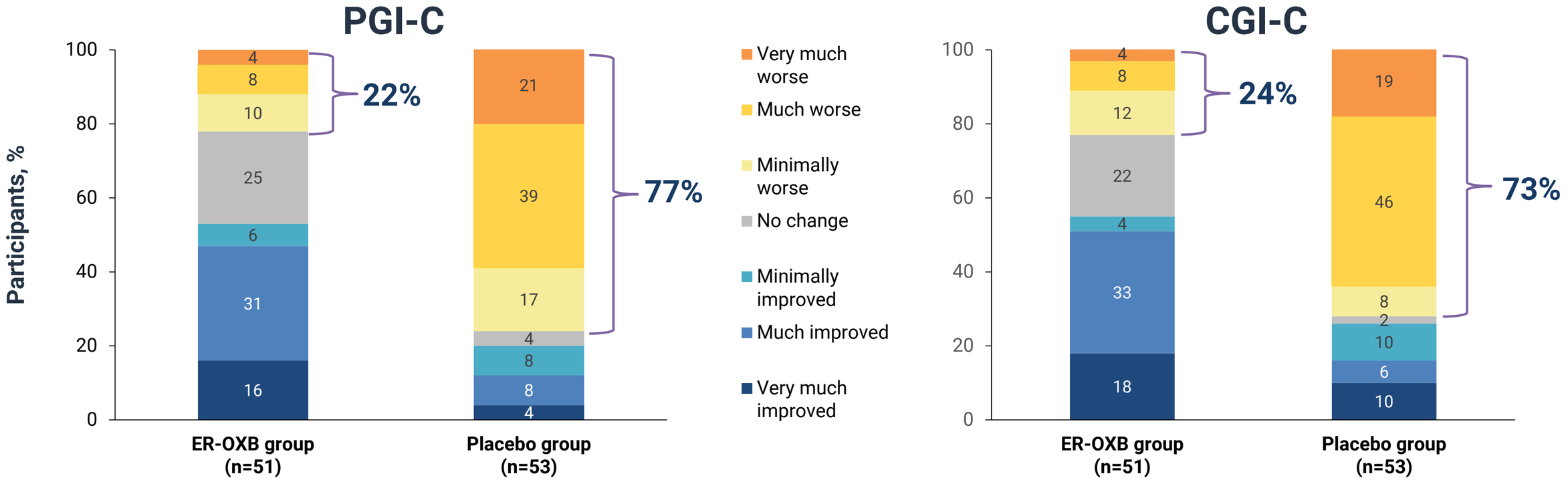
[a]Normal symptom severity is defined as an IHSS total score ≤22. (Dauvilliers Y, et al. *Neurology*. 2019;92:e1754-e1762).

[b]LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group; multiple imputation was used for 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.

Lower Risk of Worsening Global Impression Ratings with ER-OXB vs Placebo

Secondary endpoints: Worsening of PGI-C and CGI-C at end of the DBRW period for ER-OXB vs placebo



At DBRW end, marginal risk difference for ER-OXB vs placebo[a]

−0.52 (95% CI, −0.69 to −0.35)

P<0.0001

At DBRW end, marginal risk difference for ER-OXB vs placebo

−0.50 (95% CI, −0.67 to −0.33)

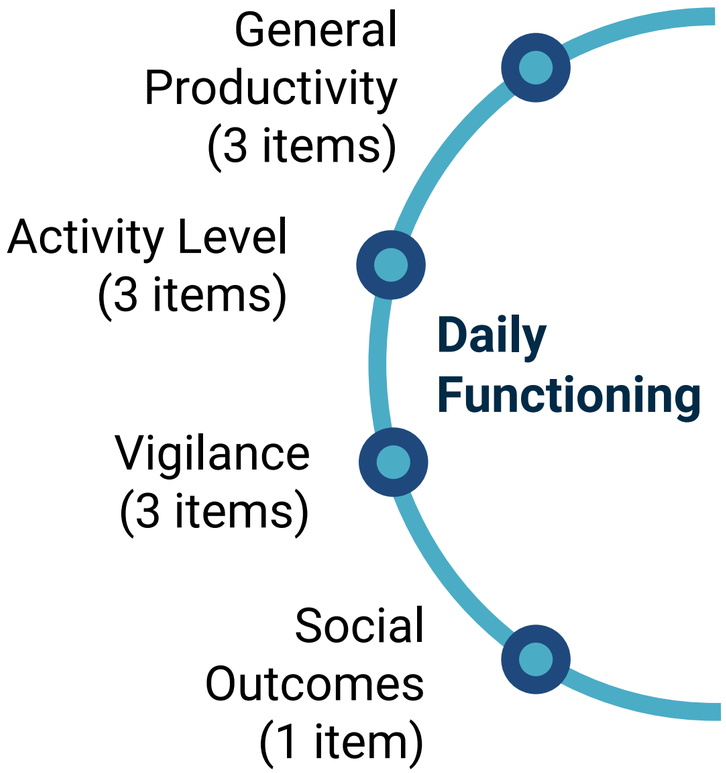
P<0.0001

Intent-to-treat population. Percentages may not sum to 100% due to rounding.

[a]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: Impact of EDS on Daily Functioning

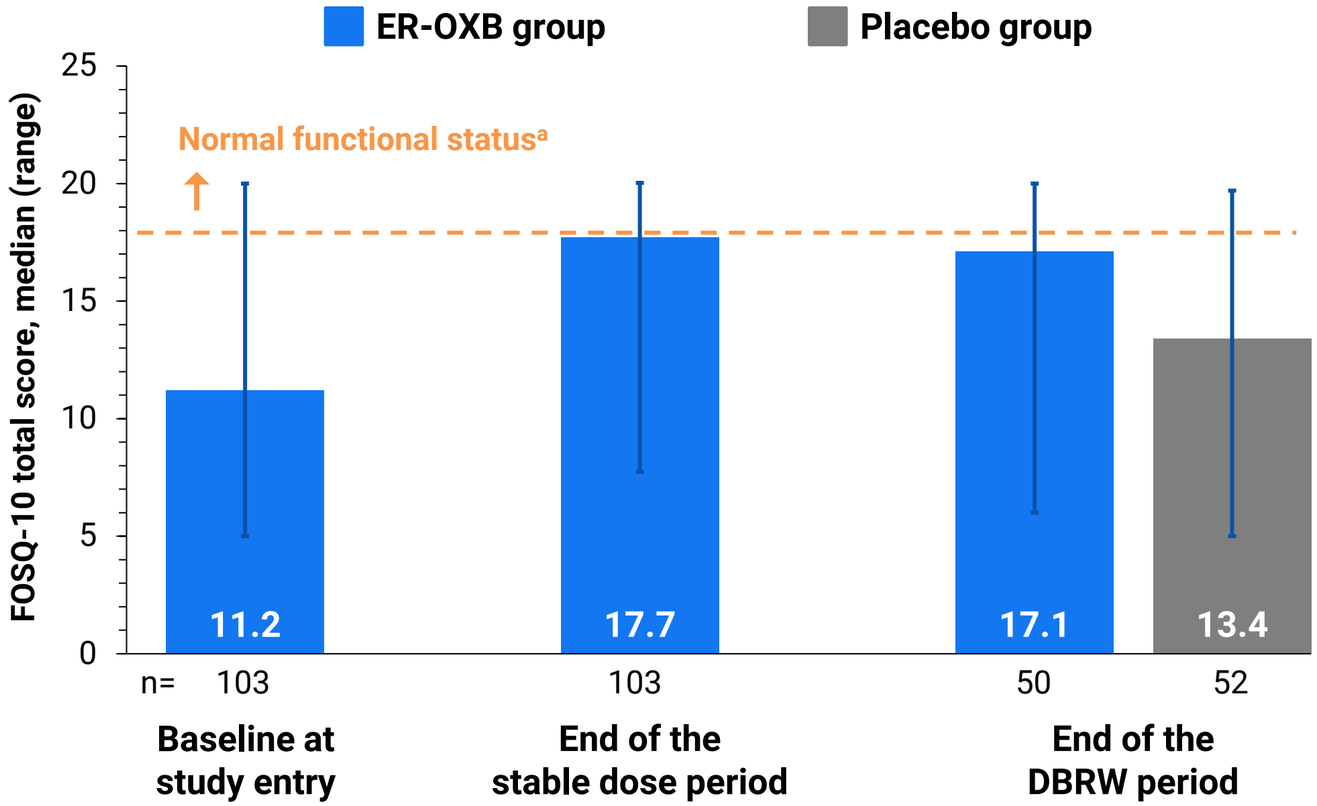


- 10-item patient-reported outcome measure assessing the impact of sleepiness on daily activities and functioning
- Scores range from 5 to 20, with higher scores indicating better functioning
- A change of **~1.7-2.0 points is generally considered clinically meaningful** in patients with sleep-wake disorders

EDS, excessive daytime sleepiness; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version.
Weaver TE, et al. *Sleep*. 1997;20(10):835-843. Chasens ER, et al. *Sleep Med*. 2009;7(4):227-234.

Improvements in Daily Functioning Maintained with ER-OXB vs Placebo

Secondary endpoint: Worsening in FOSQ-10 total scores from end of the stable dose period to end of the DBRW period

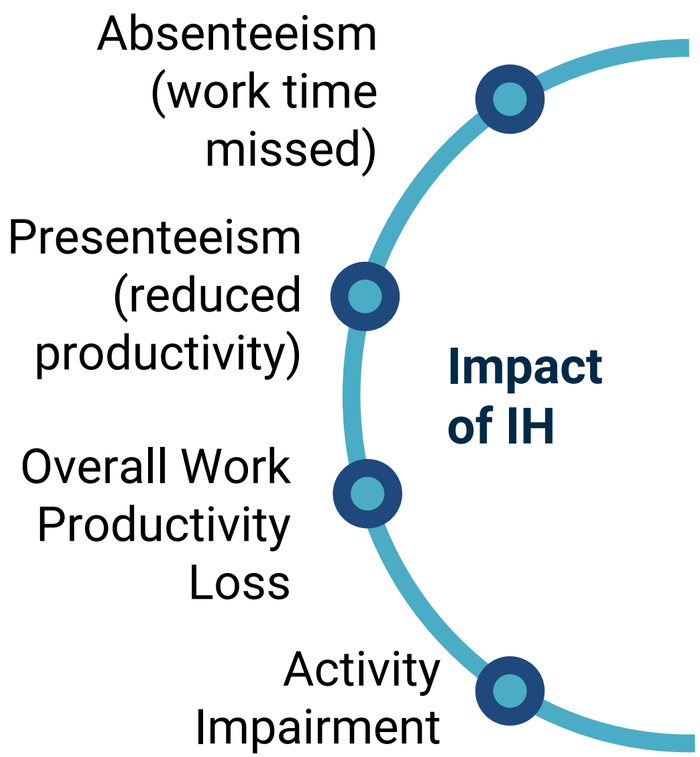


Baseline at Study Entry, median (range): 11.2 (5-20)

FOSQ-10 total score		ER-OXB group	Placebo group
End of stable dose	Participants, n	50	53
	Median (range)	18.3 (9.0-20.0)	16.7 (7.7-20.0)
End of DBRW	Participants, n	50	52
	Median (range)	17.1 (6.0-20.0)	13.4 (5.0-19.7)
	LSMD (95% CI) vs placebo (stable dose to DBRW)[b]	**2.7 (1.4-4.1) *P*=0.0001**	

Intent-to-treat population.
[a]Normal functional status, 17.9-20; functional impairment, <17.9. (Weaver TE, et al. *Sleep*. 2007; 30(6):711-719).
[b]LSMD (ER-OXB vs placebo) for the difference from 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.

WPAI:SHP: Impact of IH on Work Productivity and Daily Activities

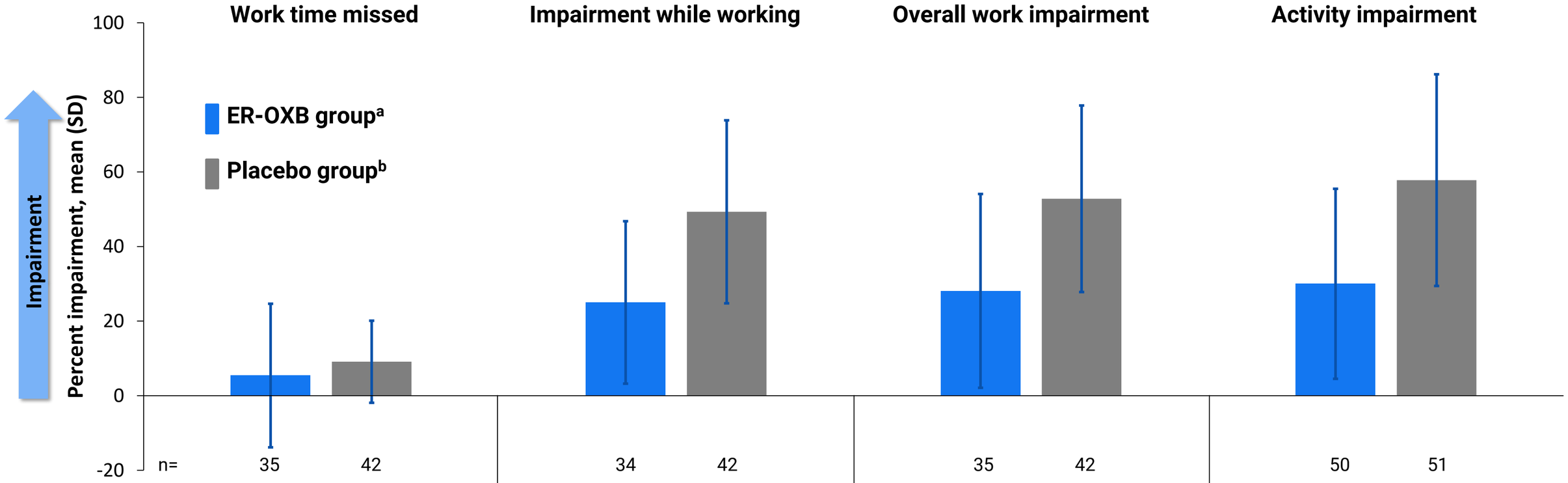


- 6-item patient-reported questionnaire assessing the impact of a specific health condition on work and daily activities over the previous 7 days
- Scores range from 0% to 100%
  - Higher percentages indicate greater impairment

Reilly MC, Zbrozek AS, Dukes EM. *Pharmacoeconomics*. 1993;4(5):353-365.
IH, idiopathic hypersomnia; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Improvement in Work and Activity Impairment Maintained with ER-OXB vs Placebo

Exploratory endpoint: Worsening in impairment on WPAI:SHP subscale from end of the stable dose period to end of the DBRW period



	Work time missed	Impairment while working	Overall work impairment	Activity impairment
LSMD (95%CI) vs placebo[c]	−2.6 (−9.8 to 4.6)	−22.8 (−32.6 to −13.0)	−21.2 (−32.2 to −10.1)	−25.5 (−35.7 to −15.3)
***P* value (nominal)**	**0.4741**	**<0.0001**	**0.0003**	**<0.0001**

Intent-to-treat population.

[a]At the end of the stable dose period, 80% (n=40) participants were employed; at the end of the DBRW period, 76% (n=38) were employed.

[b]At the end of the stable dose period, 79% (n=42) participants were employed; at the end of the DBRW period, 84% (n=43) were employed.

[c]LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group.

DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; LSMD, least squares mean difference; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

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BC-CCI-E: Patient's Perspective of Severity and Impact of Cognitive Impairment

Cognitive Impairment

Perceived Severity[1]

Items include:

- Forgetfulness/memory problems
- Poor concentration
- Trouble expressing thoughts
- Trouble finding the right word
- Slow thinking speed
- Trouble figuring things out or solving problems

Rating categories

Severe	15-18
Moderate	9-14
Mild	5 -8
None or minimal	0-4

Perceived Impact[2]

Expanded version assesses difficulty with:

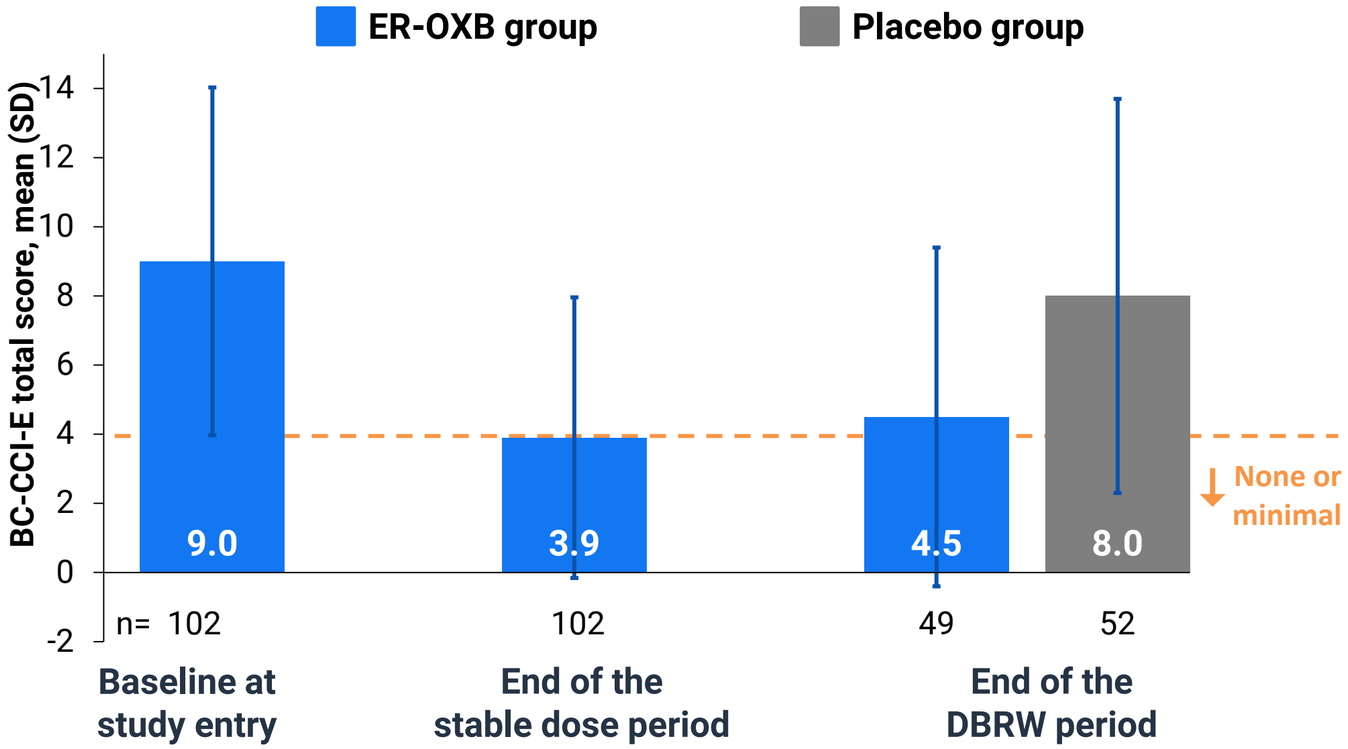
- Job
- Relationships with friends and family
- Social activities, recreational activities, or hobbies

BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded.

1. Iverson GL, Lam RW. *Ann Clin Psychiatry.* 2013;25(2):135. 2. British Columbia Cognitive Complaints Inventory (BC-CCI-E) Expanded Version Iverson GL. 2013. https://workingwithdepression.psychiatry.ubc.ca/files/2013/07/BC-CCI-Expanded-2013.pdf. Accessed October 14, 2025.

Improvements in Cognitive Impairment Maintained with ER-OXB vs Placebo

Exploratory endpoint: Worsening in BC-CCI-E total scores from end of the stable dose period to end of the DBRW period



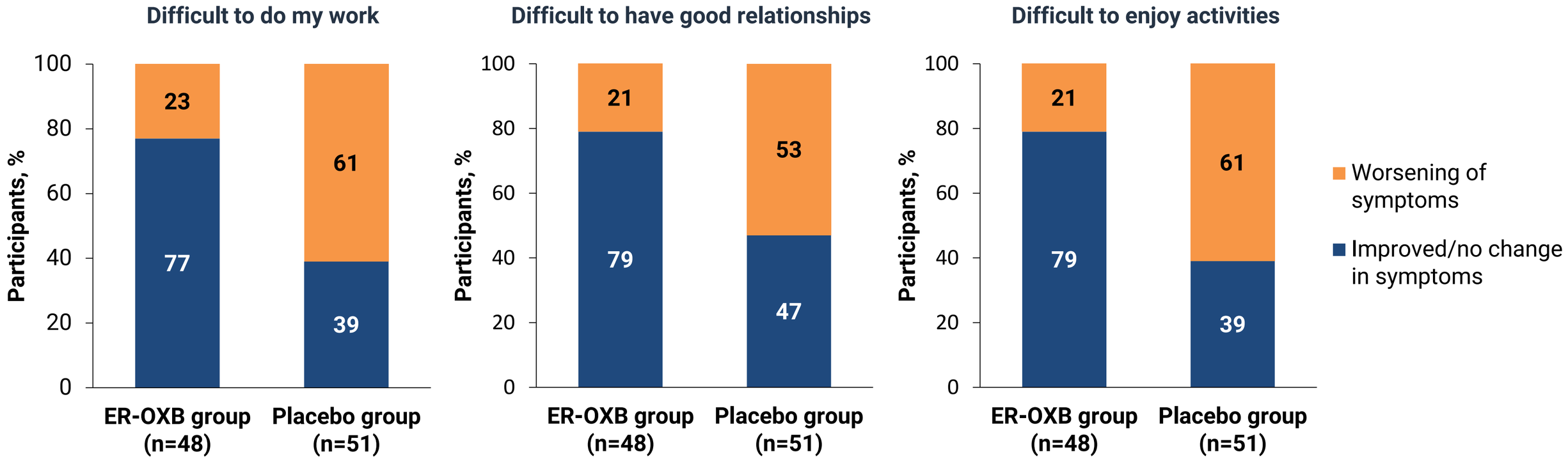
BC-CCI-E total score		ER-OXB group	Placebo group
End of stable dose	Participants, n	50	52
	Mean (SD)	3.4 (3.9)	4.4 (4.2)
End of DBRW	Participants, n	49	52
	Mean (SD)	4.5 (4.9)	8.0 (5.7)
	LSMD (95% CI) vs placebo (stable dose to DBRW)[a]	**−2.8 (−4.5 to −1.1) *P*=0.0016 (nominal)**	

Intent-to-treat population.
[a]LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group.
BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; LSMD, least squares mean difference.

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Lower Risk of Functional Impact Due to Cognitive Impairment with ER-OXB vs Placebo

Exploratory endpoint: Worsening of functional impairment on BC-CCI-E from the end of the stable dose period to the end of DBRW period



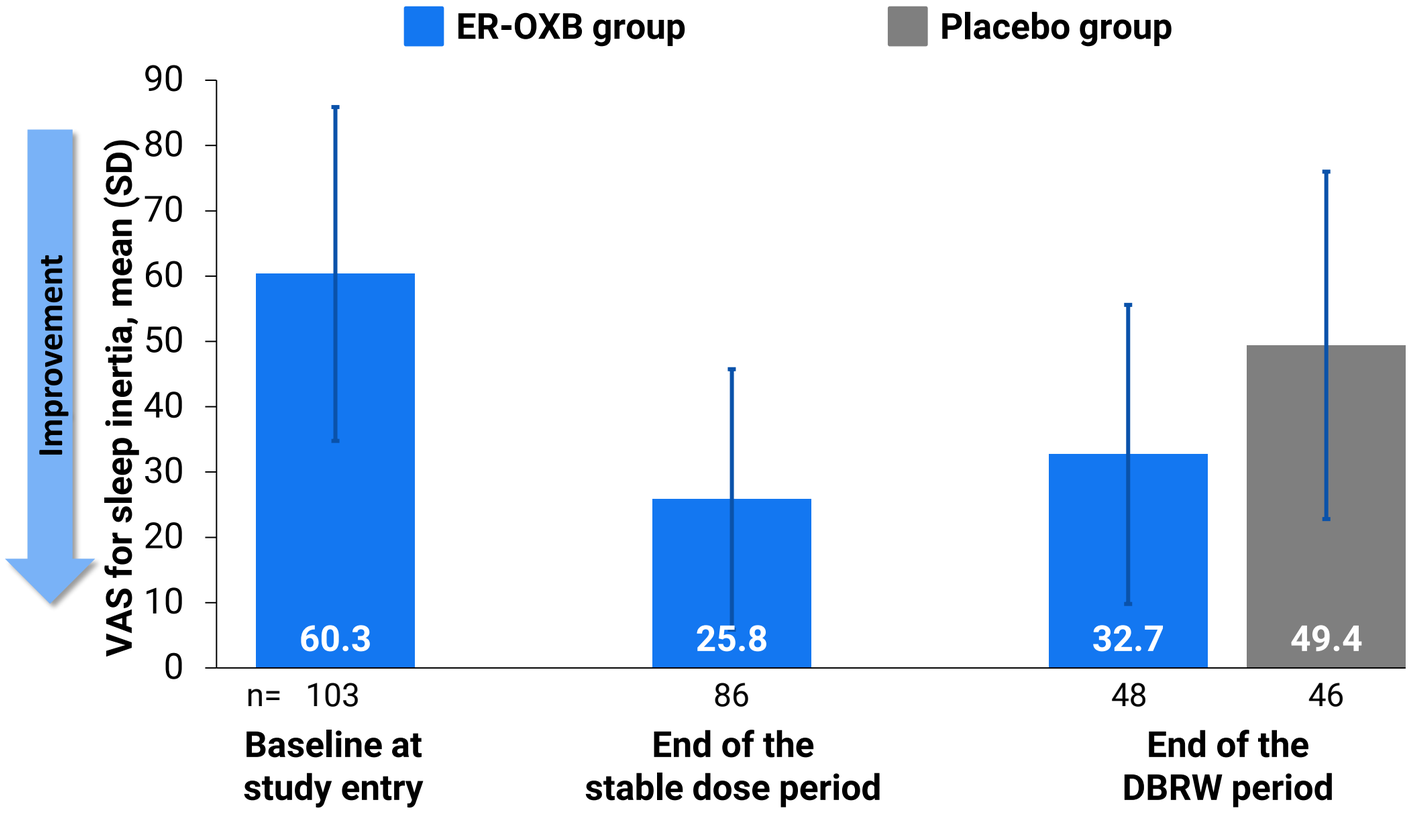
	Difficult to do my work	Difficult to have good relationships	Difficult to enjoy activities
Marginal risk difference for ER-OXB vs placebo	−0.4 (−0.6 to −0.2)	−0.3 (−0.5 to −0.1)	−0.4 (−0.6 to −0.2)
***P* value (nominal)**	**<0.0001**	**0.0005**	**<0.0001**

Intent-to-treat population.
Data reflect change from the end of the stable dose period to the end of the DBRW period.
BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate.

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Improvements in Sleep Inertia Maintained with ER-OXB vs Placebo

Exploratory endpoint: Worsening of sleep inertia on VAS from end of the stable dose period to end of the DBRW period



VAS for sleep inertia		ER-OXB group	Placebo group
End of stable dose	Participants, n	41	45
	Mean (SD)	26.4 (19.3)	25.3 (20.7)
End of DBRW	Participants, n	48	46
	Mean (SD)	32.7 (22.9)	49.4 (26.6)
	LSMD (95% CI) vs placebo (stable dose to DBRW)[a]	**−16.4 (−24.9 to −7.9) *P*=0.0003 (nominal)**	

Intent-to-treat population.
VAS scores for sleep inertia: 0=very easy to 100=very difficult.
[a]LSMD (ER-OXB vs placebo) for the difference from end of the stable dose period to the end of DBRW for each group.
DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; LSMD, least squares mean difference; VAS-SI, visual analogue scale for sleep inertia.

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Safety Over 14 Weeks of Treatment

The ER-OXB safety profile was generally consistent with previously observed safety data for ER-OXB with no new safety signals

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

ADRs[a] in ≥5% of participants overall	Overall (N=157)
Nausea	23%
Anxiety	15%
Headache	14%
Dizziness	12%
Vomiting	10%
Enuresis	6%
Tremor	6%
Decreased appetite	5%
Fatigue	5%

Safety population.
No deaths occurred.
[a]ADRs were adverse events or serious adverse events deemed possibly related or related to investigational product.
ADR, adverse drug reaction; DBRW, double-blind randomised withdrawal; ER-OXB, extended-release oxybate; OLDT, open-label dose titration; TEAE, treatment-emergent adverse event.

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Conclusions

- **REVITALYZ met the primary endpoint and secondary endpoints for EDS and symptom severity which were clinically meaningful and statistically significant**

  ✓ ESS ✓ PGI-C ✓ IHSS ✓ CGI-C ✓ FOSQ-10

- Placebo-controlled data showed clinically relevant cognitive and functional benefits with ER-OXB

  ✓ BC-CCI-E ✓ WPAI:SHP ✓ VAS-SI

  – REVITALYZ is the first placebo-controlled trial showing significant and clinically relevant changes in cognition (BC-CCI) with an oxybate in IH

- ER-OXB was generally well tolerated and aligned with the known safety profile of oxybates

A single, full therapeutic dose of ER-OXB taken once at bedtime delivered statistically significant and clinically meaningful benefits in patients with IH

BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; CGI-C, Clinical Global Impression of Change; EDS, excessive daytime sleepiness; ER-OXB, extended-release oxybate; ESS, Epworth Sleepiness Scale; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale; PGI-C, Patient Global Impression of Change; VAS-SI, visual analogue scale for sleep inertia; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

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Thank you

To the participants, families and caregivers, investigators, and study staff at all REVITALYZ sites