Improved Sleep Latency Throughout the Day With Once-Nightly Sodium Oxybate in People With Narcolepsy: Post Hoc Analysis of the Phase 3 REST-ON Trial

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3136

INTRODUCTION

- Narcolepsy is a rare, chronic neurologic disorder characterized by excessive daytime sleepiness (EDS), REM-related phenomena, and disturbed/disrupted nocturnal sleep[1,2]
- Sodium oxybate is strongly recommended by US and European guidelines for the treatment of EDS or cataplexy in adults with narcolepsy[3,4]
- Immediate-release oxybates (sodium oxybate and mixed-salt oxybates [IR-OXB])[5,6] require twice-nightly dosing; extended-release sodium oxybate (ER-OXB) is taken once at bedtime, avoiding a second nighttime dose[7]
- In the phase 3 REST-ON trial (NCT02720744), ER-OXB significantly improved mean sleep latency (MSL) on the Maintenance of Wakefulness Test (MWT) vs placebo at all doses and time points assessed (all $P<0.001$)[1]
  - Assessing nap-to-nap variability in sleep latency may help characterize the durability of ER-OXB's effect on EDS throughout the day[1]

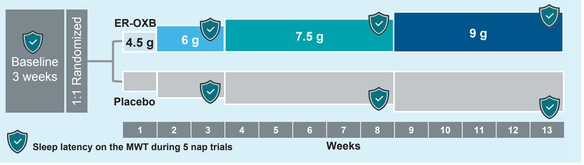
OBJECTIVE

- To assess sleep latency on the MWT for each of the 5 nap trials conducted throughout each test day during the 13-week treatment period in REST-ON

METHODS

- In REST-ON, participants aged ≥16 years with narcolepsy were randomized 1:1 to receive once-nightly ER-OXB or placebo; randomization was stratified by narcolepsy type (ie, narcolepsy type 1 [NT1] or type 2 [NT2])
- The MWT was performed at baseline, week 3, week 8, and week 13 (**Figure 1**)
  - On each test day, 5 nap trials of 30 min each were conducted; the first trial occurred ~2 h after awakening and subsequent trials occurred approximately every 2 h thereafter
  - Overall MSL (ie, 5-trial average sleep latency) and sleep latency for each individual nap trial were calculated by treatment group for each test day
- Sleep latency was analyzed using the modified intent-to-treat (mITT) population (ie, randomized participants with ≥1 efficacy measurement after receiving the 6-g dose of ER-OXB or placebo equivalent), both overall and by narcolepsy type
- For this post hoc analysis, *t* tests were used to compare mean change from baseline in sleep latency for each individual nap trial between ER-OXB and placebo at week 3 (6-g dose), week 8 (7.5-g dose), and week 13 (9-g dose) in the overall mITT population; nominal *P* values are reported

FIGURE 1: REST-ON Trial Design



ER-OXB, extended-release oxybate; MWT, Maintenance of Wakefulness Test.

RESULTS

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

- In REST-ON, 212 participants were randomized and received ≥1 dose of ER-OXB (n=107) or placebo (n=105)
- Baseline characteristics were generally balanced between treatment groups (**Table 1**)
  - Most participants were female (70%), white (75%), and had NT1 (76%)
  - As reported previously,[8] characteristics were similar between participants with NT1 and NT2, with slight differences in mean age (NT1, 32.1 y; NT2, 28.3 y) and proportions of female participants (NT1, 73%; NT2, 52%)
- The mITT population included 190 participants (ER-OXB, n=97; placebo, n=93)

TABLE 1: Baseline Demographic and Disease Characteristics (Safety Population)

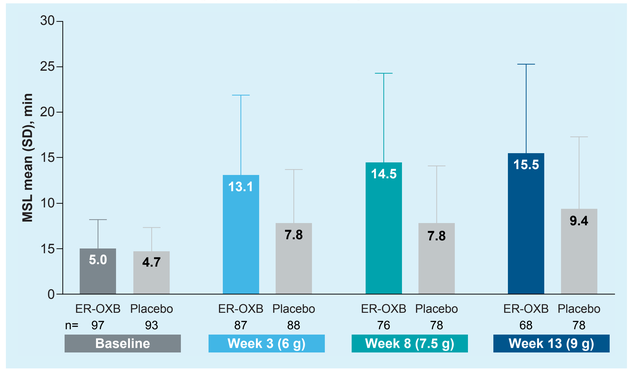
Characteristic	ER-OXB (n=107)	Placebo (n=105)
Mean (SD) age, y	31 (11)	32 (11)
Sex, n (%)		
Female	69 (64)	75 (71)
Race, n (%)		
Asian	3 (3)	8 (8)
Black or African American	21 (20)	15 (14)
Other[a]	3 (3)	2 (2)
White	80 (75)	80 (76)
Narcolepsy type, n (%)		
NT1	80 (75)	82 (78)
NT2	27 (25)	23 (22)

ER-OXB, extended-release oxybate; NT1, narcolepsy type 1; NT2 narcolepsy type 2.
[a]Egyptian (n=2); white, American Indian/Alaska Native (n=1); half Asian, half white (n=1); and multiracial (white/African American/Native American, n=1).

OVERALL MSL BY TEST DAY IN THE mITT POPULATION

- Baseline mean (SD) MSL was similar between treatment groups
- MSL increased from baseline at each time point (week 3 [6 g], week 8 [7.5 g], and week 13 [9 g]), with greater increases observed with ER-OXB vs placebo (**Figure 2**)
  - Difference in least-squares mean change from baseline in MSL for ER-OXB vs placebo was significant at each time point (all $P<0.001$)[1]

FIGURE 2: Overall MSL by Test Day (mITT Population)

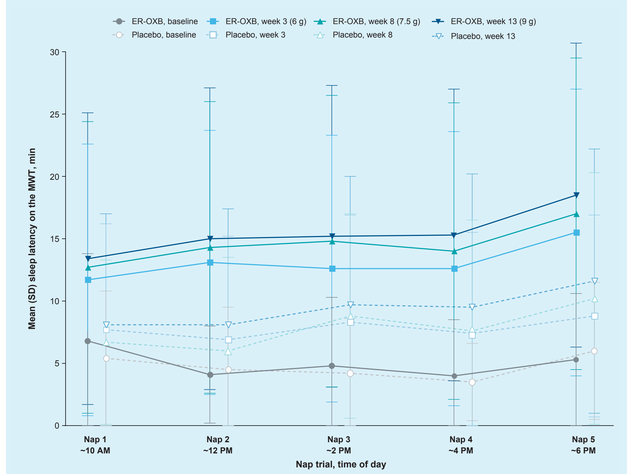


ER-OXB, extended-release oxybate; mITT, modified intent-to-treat; MSL, mean sleep latency.

SLEEP LATENCY BY NAP TRIAL IN THE mITT POPULATION

- Baseline mean sleep latencies across nap trials were similar between treatment groups
- ER-OXB improved sleep latency vs placebo across all 5 nap trials at all assessed doses/time points; changes from baseline favored ER-OXB with nominal $P<0.05$, except during nap trial 1 at week 3 (**Figure 3**)
- The longest sleep latency and greatest improvement vs placebo occurred in the 5th nap trial (~10 h after waking) on each test day (all nominal $P<0.0001$)

FIGURE 3: Sleep Latency by Nap Trial (mITT Population)



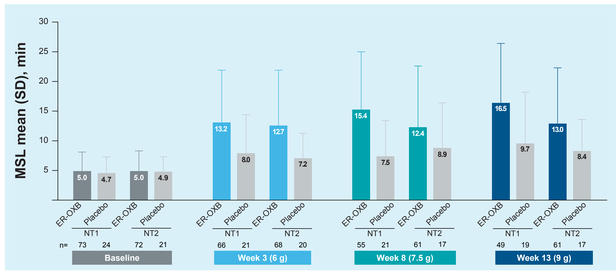
Time point	Treatment	Participants, n	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5
Baseline	ER-OXB	96	6.8 (7.0)	4.1 (3.9)	4.8 (5.5)	4.0 (4.5)	5.3 (5.3)
	Placebo	93	5.4 (5.4)	4.5 (5.0)	4.2 (4.4)	4.2 (4.4)	6.0 (5.5)
Change from baseline: Week 3	ER-OXB	87	4.8 (12.0)	9.0 (10.7)****	7.7 (11.3)*	8.7 (11.3)**	10.5 (10.7)****
	Placebo	88	2.2 (7.6)	2.4 (9.8)	4.1 (8.4)	3.9 (7.8)	2.8 (8.2)
Change from baseline: Week 8	ER-OXB	75	6.1 (12.9)**	10.2 (11.5)****	10.0 (11.9)***	9.9 (11.6)***	11.8 (11.8)****
	Placebo	78	1.2 (7.5)	1.3 (9.4)	4.4 (7.9)	4.0 (7.9)	3.9 (9.3)
Change from baseline: Week 13	ER-OXB	68	6.4 (12.0)*	10.9 (12.3)***	10.7 (12.0)**	11.1 (10.9)**	13.1 (11.4)****
	Placebo	78	2.6 (9.9)	3.5 (10.9)	5.3 (8.9)	5.9 (9.8)	5.1 (11.3)

In the table, baseline values represent mean (SD); post-baseline values (Weeks 3, 8, and 13) represent mean (SD) change from baseline.
ER-OXB, extended-release oxybate; mITT, modified intent-to-treat; MWT, Maintenance of Wakefulness Test.
*Nominal $P<0.05$ for change from baseline in ER-OXB vs placebo; **Nominal $P<0.01$ for change from baseline in ER-OXB vs placebo; ***Nominal $P<0.001$ for change from baseline in ER-OXB vs placebo; ****Nominal $P<0.0001$ for change from baseline in ER-OXB vs placebo.

OVERALL MSL BY TEST DAY FOR PARTICIPANTS WITH NT1 AND NT2

- Across treatment groups, participants with NT1 and NT2 had similar MSL at baseline (4.7-5.0 min; **Figure 4**)
- MSL on each test day trended toward progressive increase from baseline through week 13 (9 g) with ER-OXB in both NT1 and NT2 participants, with greater numerical increases vs placebo at all time points

FIGURE 4: Overall MSL by Test Day for Participants With NT1 and NT2

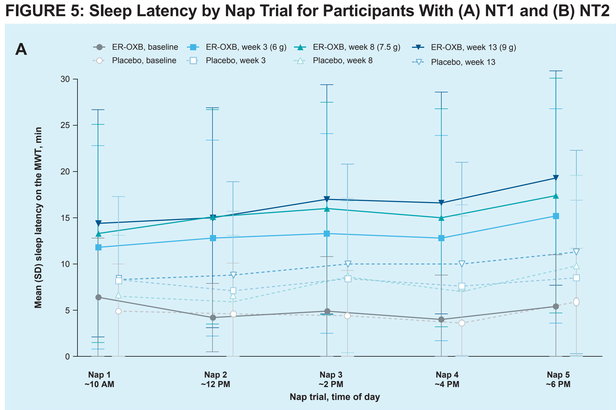


ER-OXB, extended-release oxybate; MSL, mean sleep latency; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

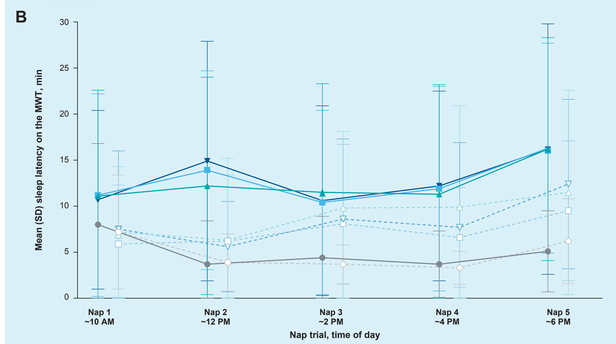
SLEEP LATENCY BY NAP TRIAL IN PARTICIPANTS WITH NT1 AND NT2

- Baseline per-nap sleep latencies were similar across all treatment groups
- In participants with NT1, sleep latency showed modest within-day variation with an evening peak (nap 5, ~6 PM) for those receiving ER-OXB (**Figure 5A**)
- In participants with NT2, the diurnal profile was more variable (**Figure 5B**)
  - Sleep latency was similar across time points for both treatment groups; no ER-OXB dose response was observed for per-nap sleep latency in participants with NT2
- Numerical improvements from baseline in sleep latency were greater with ER-OXB vs placebo across all nap trials and time points in both NT1 and NT2 subgroups

FIGURE 5: Sleep Latency by Nap Trial for Participants With (A) NT1 and (B) NT2



Time point	Treatment	Participants, n	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5
Baseline	ER-OXB	72	6.4 (6.4)	4.2 (3.7)	4.9 (5.9)	4.0 (4.8)	5.4 (5.6)
	Placebo	72	4.9 (5.1)	4.6 (5.5)	4.4 (4.9)	3.6 (3.5)	5.9 (5.8)
Change from baseline: Week 3	ER-OXB	66	5.4 (11.2)	8.6 (10.5)	8.2 (11.9)	9.0 (11.4)	10.3 (10.8)
	Placebo	67	3.3 (7.4)	2.4 (10.2)	4.1 (8.4)	4.0 (8.4)	2.7 (8.5)
Change from baseline: Week 8	ER-OXB	54	6.8 (12.8)	10.8 (11.2)	10.9 (12.3)	10.7 (11.8)	12.1 (11.9)
	Placebo	61	1.7 (7.0)	1.1 (9.3)	3.9 (7.8)	3.3 (6.8)	3.6 (8.0)
Change from baseline: Week 13	ER-OXB	49	7.9 (12.3)	10.9 (11.7)	12.5 (12.7)	12.1 (11.1)	14.0 (11.0)
	Placebo	61	3.5 (9.5)	4.1 (12.0)	5.5 (9.1)	6.4 (9.8)	5.0 (11.4)



Time point	Treatment	Participants, n	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5
Baseline	ER-OXB	23	8.0 (8.8)	3.7 (4.7)	4.4 (4.5)	3.7 (3.6)	5.1 (4.4)
	Placebo	21	7.2 (6.2)	3.9 (3.1)	3.7 (2.1)	3.3 (1.8)	6.2 (4.6)
Change from baseline: Week 3	ER-OXB	21	2.9 (14.4)	10.3 (11.2)	6.1 (9.0)	7.9 (11.3)	11.2 (10.7)
	Placebo	20	-1.6 (6.9)	2.2 (8.4)	4.4 (8.6)	3.3 (5.4)	3.2 (7.3)
Change from baseline: Week 8	ER-OXB	20	4.2 (13.5)	8.6 (12.3)	7.4 (10.7)	7.9 (11.4)	11.1 (11.9)
	Placebo	17	−0.7 (9.2)	2.2 (10.2)	6.1 (8.2)	6.5 (10.8)	4.8 (13.1)
Change from baseline: Week 13	ER-OXB	19	2.5 (10.4)	10.8 (14.2)	6.2 (8.6)	8.4 (10.2)	10.8 (12.5)
	Placebo	17	−0.8 (11.1)	1.1 (5.4)	4.7 (8.6)	4.2 (9.9)	5.7 (11.4)

In the table, baseline values represent mean (SD); post-baseline values (Weeks 3, 8, and 13) represent mean (SD) change from baseline.
ER-OXB, extended-release oxybate; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

STUDY LIMITATIONS

- This was a post hoc analysis and the per-nap comparisons were not pre-specified; *P* values reported for per-nap comparisons in the mITT population are nominal, were used for descriptive purposes only, and should not be interpreted as confirmatory
- The overall mITT population was enriched for participants with NT1 to analyze a coprimary endpoint of REST-ON (ie, the number of cataplexy episodes)
  - Smaller subgroups (ie, participants with NT2) may limit the ability to detect differences between treatment groups and clinical conclusions that can be drawn for these populations

CONCLUSIONS

- ER-OXB significantly improved overall MSL on the MWT vs placebo at all assessed doses and time points
- Numerical improvements in overall MSL and sleep latency for each individual MWT nap trial were evident by week 3 (6 g) and continued to increase through week 13 (9 g)
- Treatment with ER-OXB resulted in improved wakefulness and reduced daytime sleepiness in people with narcolepsy that persisted throughout the day
  - MSL was the longest during the last nap trial on each test day, occurring in the evening approximately 10 h after awakening (~6 PM) for all doses and time points tested
  - Findings were consistent regardless of narcolepsy subtype; diurnal variation between subgroups may reflect inherent differences in disease phenotypes
- Taken together, these results suggest that once-nightly dosing of ER-OXB provides clinically meaningful[3] improvements in EDS that persist throughout the day and into the evening hours

KEY TAKEAWAYS

- In a post hoc analysis, ER-OXB taken once at bedtime improved daytime sleepiness experienced by people with NT1 and NT2
- Clinically meaningful improvement in wakefulness persisted throughout the day into the evening hours, through ~10 h after awakening

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DISCLOSURES

MJT has served as a consultant or on advisory boards for Alkermes, Inc., Avadel Pharmaceuticals, Axsome Therapeutics, Balance Therapeutics, Centessa Pharmaceuticals, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, NLS Pharmaceuticals, Suven Life Sciences Ltd., and Takeda Pharmaceutical Co. **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. **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. **LBH** has participated in clinical research for Alkermes, Inc., Axsome Therapeutics, Avadel Pharmaceuticals, Breas Medical, Centessa Pharmaceuticals, Eisai, Fisher & Paykel Healthcare, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Lilly, LivaNova/OSPREY, Merck & Co., Noctrix Health, Samsung, Sanofi, Suven Life Sciences Ltd., Takeda Pharmaceutical Co., and Vanda Pharmaceuticals and served as speaker or consultant for Avadel Pharmaceuticals, Axsome Therapeutics, Fisher & Paykel Healthcare, Harmony Biosciences, Jazz Pharmaceuticals, Noctrix Health, and Takeda Pharmaceutical Co. **LEO** has served on advisory boards for Avadel Pharmaceuticals, Harmony Biosciences, and Jazz Pharmaceuticals. **JB** is an employee of Alkermes, Inc. **YD** has served as a consultant/advisory board member for Alkermes, Inc., Avadel Pharmaceuticals, Bioprojet, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Centessa Pharmaceuticals, and Takeda Pharmaceutical Co.

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