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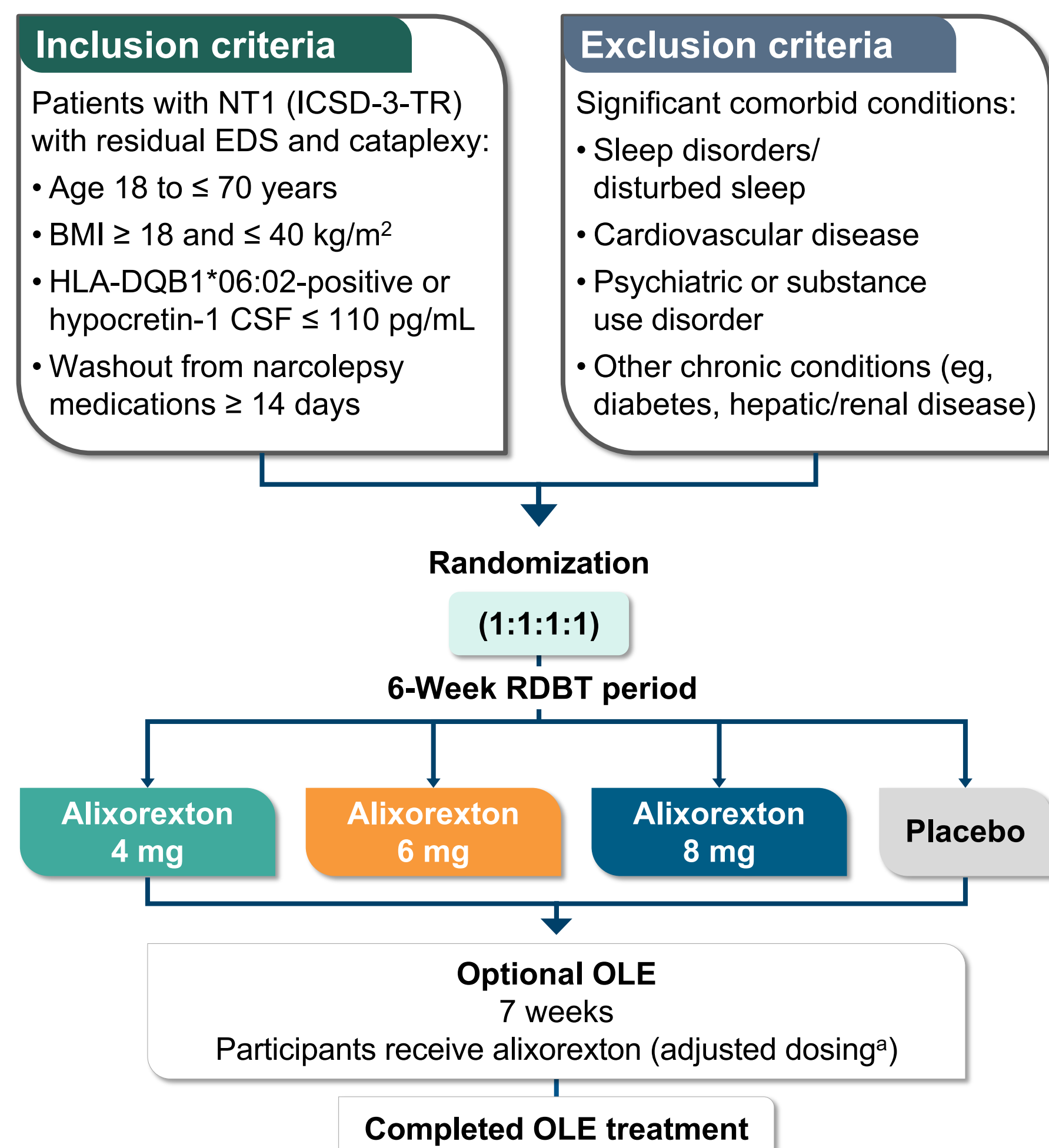
Introduction

- Narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness (EDS), cataplexy, sleep hallucinations, sleep paralysis, and disrupted nighttime sleep.^{1,2}
- The pathophysiology of NT1 involves loss of orexin neurons, which project to brain regions that affect wakefulness, arousal, and cognition³
- Alixorexton (ALKS 2680) is a highly potent, oral, selective orexin 2 receptor (OX2R) agonist under development as a treatment for narcolepsy and idiopathic hypersomnia^{4,5}
- In a phase 1b study, alixorexton was generally well tolerated and improved wakefulness in participants with NT1, narcolepsy type 2, and idiopathic hypersomnia^{4,5}
- The randomized, phase 2 Vibrance-1 study (NCT06358950) examined the safety and efficacy of alixorexton in patients with NT1

Methods

- Vibrance-1 was a phase 2, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study conducted in the United States, Europe, and Australia evaluating oral, once-daily alixorexton (Figure 1)
- Efficacy assessments included the Maintenance of Wakefulness Test (MWT; primary), Epworth Sleepiness Scale (ESS; key secondary), and weekly cataplexy rate (WCR; key secondary); safety monitoring (secondary) included treatment-emergent adverse event (TEAE) incidence
 - The MWT is designed to assess a patient's ability to stay awake in nonstimulating conditions over a set period of time
 - The ESS is an 8-item questionnaire filled out by the patient to evaluate their chances of falling asleep while engaging in different activities
 - Cataplexy rate was calculated weekly by averaging reported cataplexy incidence over the preceding 2 weeks except for week 13, which comprises 1 week
- In this presentation, participants are shown throughout the open-label extension (OLE) by their original randomized double-blind treatment (RDBT) period randomization assignment

Figure 1. Study design



^aAll participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. BMI, body mass index; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ICSD-3-TR, International Classification of Sleep Disorders, Third Edition, Text Revision; NT1, narcolepsy type 1; OLE, open-label extension; RDBT, randomized double-blind treatment.

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Results

- Overall, 92 participants were randomly assigned to treatment (placebo: 23; alixorexton 4 mg: 23; alixorexton 6 mg: 22; alixorexton 8 mg: 24; Table 1)
- Ninety-one (99%) completed the RDBT period, with one participant discontinuing the study due to an adverse event; 90 (98%) subsequently entered the OLE, during which one participant discontinued the study due to an adverse event, one was lost to follow-up, and one withdrew from the study
- Participants had a mean age of 33.5 years, most (62%) were female, over one-third (38%) were white, and average body mass index was 28.4 kg/m²

Table 1. Participant disposition and baseline clinical characteristics

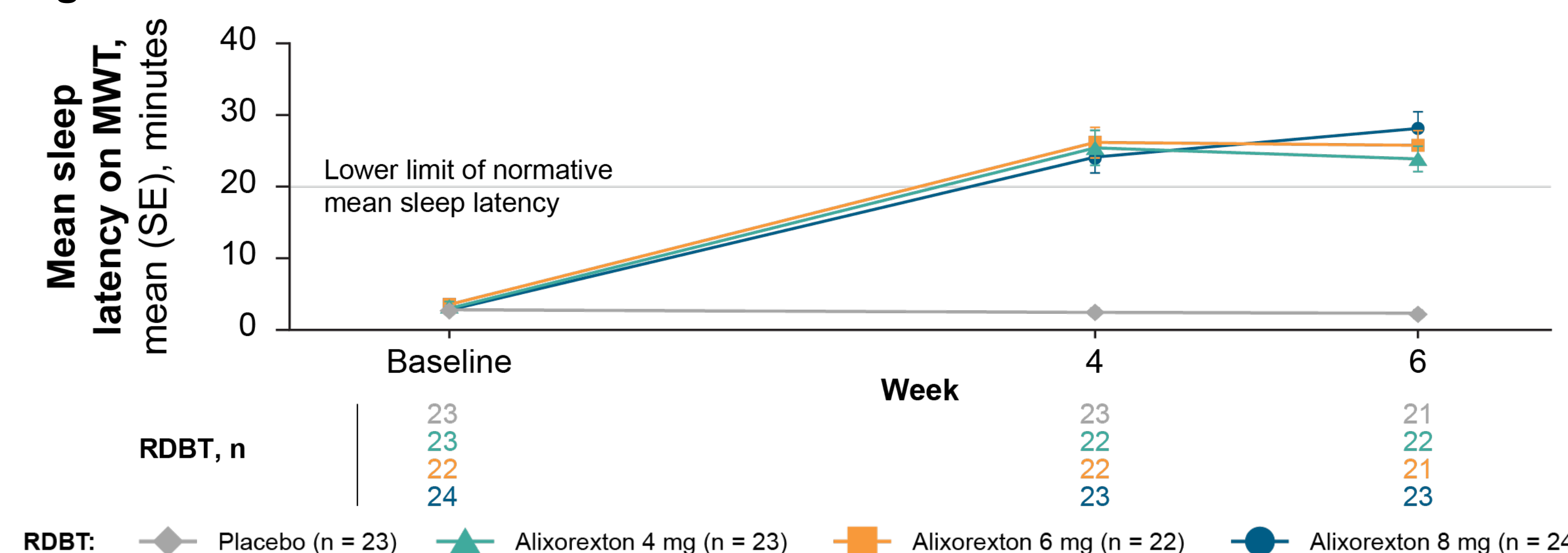
	RDBT assignment					
	Placebo (n = 23)	Alixorexton 4 mg (n = 23)	Alixorexton 6 mg (n = 22)	Alixorexton 8 mg (n = 24)	Total (N = 92)	
Disease severity						
MSL on MWT (minutes), mean (SD)	2.8 (3.1)	3.3 (3.3)	3.4 (3.2)	2.8 (2.9)	3.1 (3.1)	
ESS, mean (SD)	18.7 (2.7)	18.2 (2.5)	18.5 (3.1)	18.7 (4.0)	18.5 (3.1)	
WCR ^a	Mean (SD)	26.6 (29.9)	37.8 (53.5)	16.8 (9.8)	23.0 (17.3)	26.11 (32.6)
	Median	14.0	20.5	15.1	15.9	16.8
	[min, max]	[1.6, 121.0]	[4.7, 255.0]	[5.0, 49.0]	[1.4, 67.5]	[1.4, 255.0]
Participant disposition						
Completed week 6 visit, n (%)	23 (100)	23 (100)	22 (100)	23 (96)	91 (99)	
Completed week 13 visit, n (%)	21 (91)	23 (100)	22 (100)	22 (92)	88 (96)	

^aBaseline WCR calculated as the average weekly cataplexy rate over 2 weeks prior to first dose of study drug. ESS, Epworth Sleepiness Scale; max, maximum; min, minimum; MSL, mean sleep latency; MWT, Maintenance of Wakefulness Test; RDBT, randomized double-blind treatment; SD, standard deviation; WCR, weekly cataplexy rate.

Primary endpoint

- The mean observed values for mean sleep latency on the MWT for all alixorexton dose groups were within the normative range (≥ 20 minutes) at weeks 4 and 6 (Figure 2)
- Participants taking alixorexton at all doses had significantly improved scores from baseline to week 6 versus placebo (adjusted $P < 0.01$ for all comparisons)

Figure 2. Scores for the MSL on the MWT^a



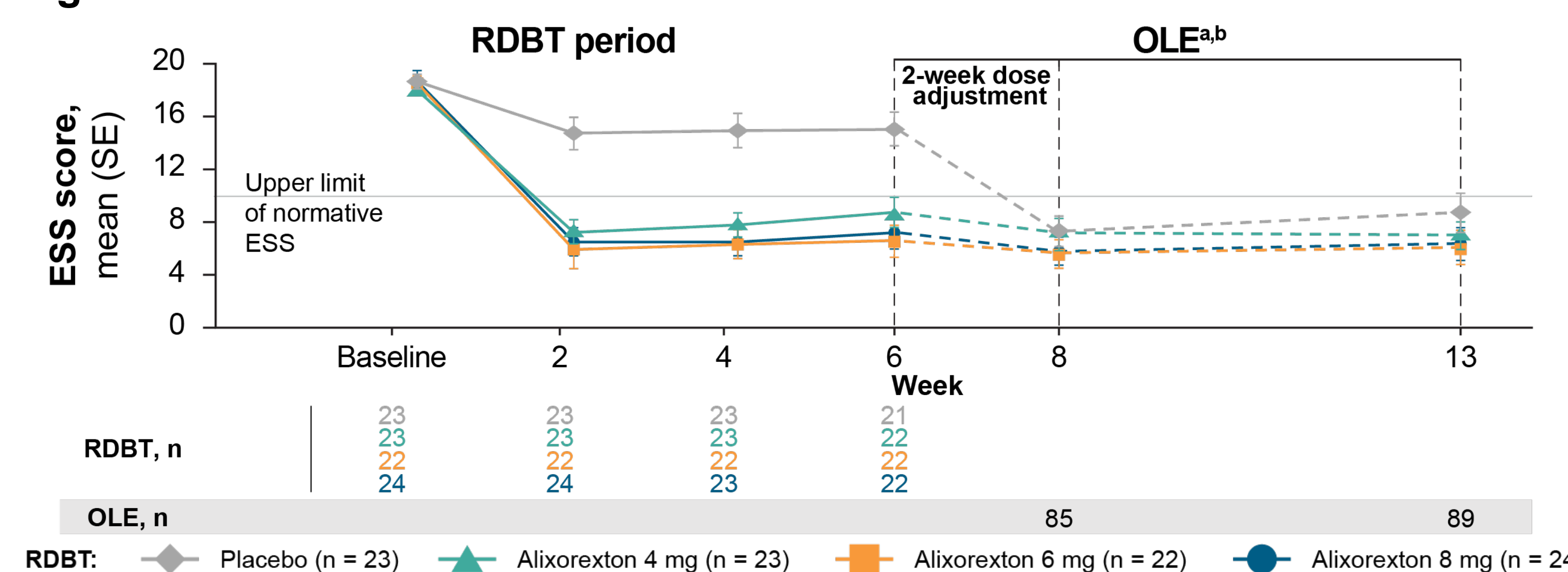
	Alixorexton			
	4 mg	6 mg	8 mg	Total
Primary endpoint: Change in MSL on the MWT from baseline to week 6	22.2	24.1	26.0	24.1
LSM change from baseline at week 6 vs placebo (95% CI) ^b	(17.2, 27.2)	(19.0, 29.1)	(21.0, 31.0)	
P value (adjusted for multiplicity)	0.01	< 0.0001	< 0.0001	

^aMWT was not collected during the OLE. ^bMissing data were imputed using multiple imputation. CI, confidence interval; LSM, least-square means; MSL, mean sleep latency; MWT, Maintenance of Wakefulness Test; OLE, open-label extension; SE, standard error.

Key secondary endpoints

- ESS scores decreased in all alixorexton dose groups starting at the first post-baseline assessment. The mean observed ESS scores fell within the range of normality (< 10)⁶ for all alixorexton dose groups at all post-baseline assessments (Figure 3)
- Participants taking alixorexton at all doses had significantly improved scores from baseline to week 6 versus placebo (adjusted $P < 0.01$ for all comparisons). Mean values during the OLE remained consistent with those observed at the end of the RDBT period

Figure 3. Scores for the ESS



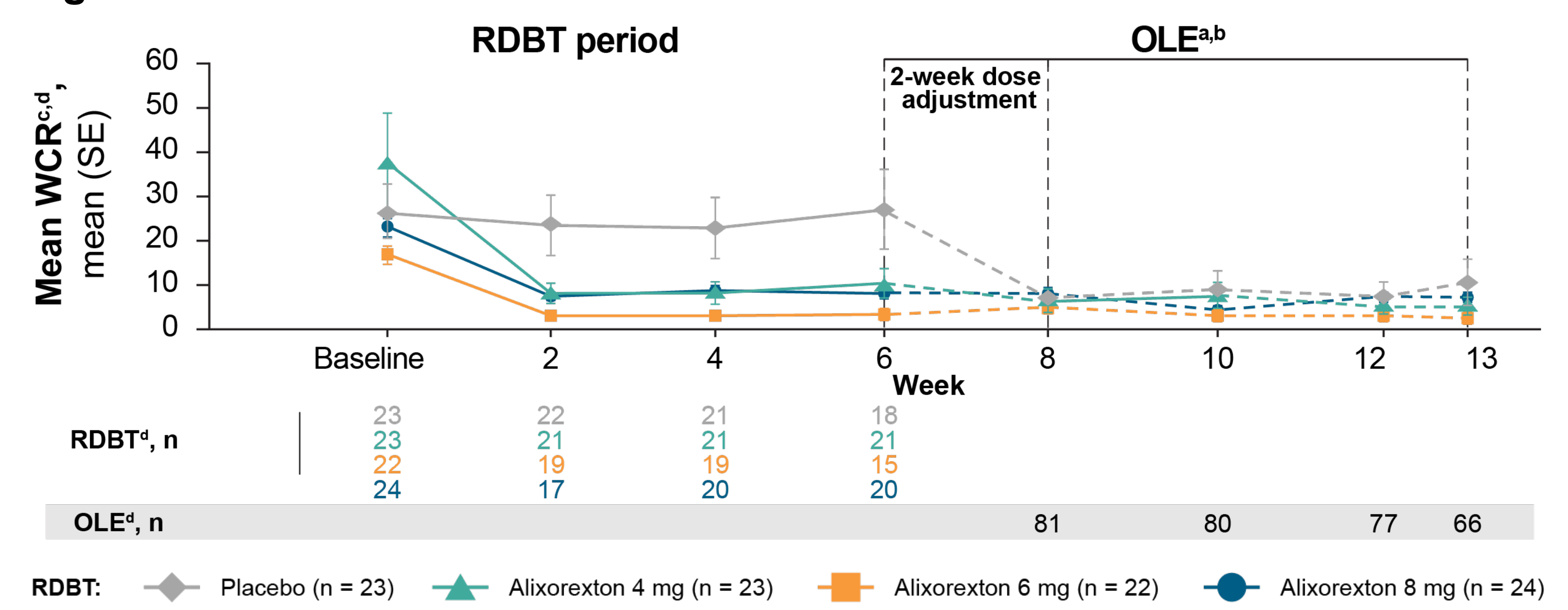
	Alixorexton			
	4 mg	6 mg	8 mg	Total
Key secondary endpoint: Change in ESS from baseline to week 6	-6.4	-8.7	-8.3	-7.8
LSM change from baseline at week 6 vs placebo (95% CI) ^b	(-9.6, -3.3)	(-11.9, -5.5)	(-11.4, -5.2)	
P value (adjusted for multiplicity)	0.01	< 0.0001	< 0.0001	

^aAll participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment. ^bDashed vertical lines indicate the beginning of the OLE (week 6), the end of the 2-week dose adjustment period (week 8), and the end of the OLE (week 13). ^cMissing data were imputed using multiple imputation. CI, confidence interval; ESS, Epworth Sleepiness Scale; LSM, least-square means; OLE, open-label extension; SE, standard error.

Disclosures
VD received institutional funding from Alkermes; participated on advisory boards for Avadel, Bioprogect, Centessa, Harmony Biosciences, Jazz Pharmaceuticals, and Takeda. RRG received speaker fees from Eisai and SomnoMed; institutional funding from Alkermes, Lilly, Takeda, and Vanda; participated on advisory boards for Apnimed and Lilly. EM received research funding from Avadel, Alkermes, Eisai, Jazz Pharmaceuticals, Takeda, and Vanda. GJL received consulting fees from Alkermes, Bioprogect, Daiichi Sankyo, Eisai, and Takeda. DTP participated on advisory boards for Addium Bio LLC, Alkermes, Centessa, Harmony Biosciences, Jazz Pharmaceuticals, Takeda, and Teva. EB has no conflicts to disclose. RdRV participated on advisory boards for Alkermes, Takeda, and Bioprogect. HC, CH, BR, JH, and JMD are employees and shareholders of Alkermes. GP received research funding from Bioprogect, Centessa, Idorsia, Jazz Pharmaceuticals, Orexia Therapeutics, and Takeda.

- Mean incidence rate ratios of WCR versus placebo ranged from 0.31 to 0.64 in the 3 alixorexton-treated groups (4, 6, and 8 mg), with statistical significance versus placebo achieved with 6 mg alixorexton (adjusted $P < 0.01$; Figure 4)
- WCR improvements observed during the OLE were consistent with those demonstrated during the randomized controlled period
- In an exploratory analysis, participants who received 6 mg or 8 mg alixorexton were cataplexy-free, on average, 71% and 69% of days during week 6, respectively, and more than 40% of participants in the 6 mg and 8 mg groups reported absence of cataplexy events during week 6

Figure 4. WCR events



Key secondary endpoint: Mean WCR at week 6	Alixorexton		
	4 mg	6 mg	8 mg
WCR incident ratio at week 6 vs placebo (95% CI) ^{a,b}	0.49 (0.23, 1.05)	0.31 (0.14, 0.70)	0.64 (0.30, 1.41)
P value (adjusted for multiplicity)	0.169	0.01	0.452

^aAll participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment. ^bDashed vertical lines indicate the beginning of the OLE (week 6), the end of the 2-week dose adjustment period (week 8), and the end of the OLE (week 13). ^cWCR data represent averages of the preceding 2 weeks except for week 13, which comprises 1 week. ^dThe minimum required number of cataplexy diaries was 10 days bi-weekly during the RDBT period, 8 days bi-weekly during the OLE period, and 4 days during week 13. ^eMissing data were imputed using multiple imputation. CI, confidence interval; OLE, open-label extension; SE, standard error; WCR, weekly cataplexy rate.

Safety endpoints

- Most TEAEs during the RDBT period and OLE were mild to moderate, and no serious TEAEs were reported during the study (Table 2)
- TEAEs reported in the OLE were generally consistent with those observed during the RDBT period, and the most common TEAEs were observed in participants transitioning from placebo to alixorexton 6 mg

Table 2. TEAEs in the RDBT period and the OLE

	RDBT period					OLE alixorexton ^a				
	Placebo (n = 23)	4 mg (n = 23)	6 mg (n = 22)	8 mg (n = 24)	Total (n = 69)	Placebo (n = 23)	4 mg (n = 23)	6 mg (n = 22)	8 mg (n = 22)	Total (N = 90)
Participants with any TEAEs^b	11 (48)	20 (87)	20 (91)	21 (88)	61 (88)	19 (83)	15 (65)	10 (46)	12 (55)	56 (62)
Participants with TEAEs related to study drug^c	6 (26)	18 (78)	17 (77)	19 (79)	54 (78)	16 (70)	9 (39)	5 (23)	6 (27)	36 (40)
TEAEs by highest severity^d										
Mild	8 (35)	13 (57)	15 (68)	11 (46)	39 (57)	10 (44)	9 (39)	6 (27)	11 (50)	36 (40)
Moderate	3 (13)	6 (26)	5 (23)	8 (33)	19 (28)	8 (35)	6 (26)	4 (18)	1 (5)	19 (21)
Severe ^e	0	1 (4)	0	2 (8)	3 (4)	1 (4)	0	0	0	1 (1)
TEAEs in ≥ 10% of all participants treated with alixorexton in the RDBT period^f										
Pollakiuria	1 (4)	15 (65)	11 (50)	12 (50)	38 (55)	10 (44)	4 (17)	2 (9)	0	16 (18)
Insomnia	0	4 (17)	7 (32)	8 (33)	19 (28)	9 (39)	1 (4)	1 (5)	0	11 (12)
Salivary hypersecretion	0	5 (22)	5 (23)	7 (29)	17 (25)	6 (26)	1 (4)	0	1 (5)	8 (9)
Micturition urgency	1 (4)	2 (9)	4 (18)	4 (17)	10 (15)	3 (13)	1 (4)	0	1 (5)	5 (6)
Vision blurred	1 (4)	2 (9)	1 (5)	7 (29)	10 (15)	3 (13)	0	1 (5)	1 (5)	5 (6)
TEAEs leading to discontinuation of study drug^g	0	0	0	1 (4)	1 (1)	2 (9)	0	0	0	2 (2)

^aAll participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment. ^bValues denote number of participants experiencing a TEAE. ^cRelationship to study drug determined by the investigator. ^dIf a participant had multiple TEAEs, the highest severity was counted. ^eSevere TEAEs included insomnia (n = 3; 1 participant taking 4 mg and 1 participant taking 8 mg during the RDBT period, 1 participant taking 6 mg during the OLE [previously placebo]), and events of tachycardia, vision blurred, and increased blood pressure that occurred in 1 participant (8 mg). ^fTEAEs by MedDRA Preferred Term. ^gThree participants discontinued study drug due to TEAEs: 1 (8 mg) during the RDBT period had TEAEs of tachycardia, vision blurred, and increased blood pressure that resolved after discontinuation; 2 (both placebo → 6 mg) discontinued during the OLE due to TEAEs of depressed mood and depression, respectively. Prior to study washout, participants were treated with escitalopram and venlafaxine, respectively. MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; RDBT, randomized double-blind treatment; TEAE, treatment-emergent adverse event.

Conclusions

- At all doses, alixorexton:
 - Provided statistically significant, clinically meaningful improvements in objective wakefulness and patient-reported sleepiness at week 6; improvements were maintained through week 13
 - Led to clinically meaningful improvements in cataplexy, with statistically significant improvement seen at week 6 at the 6 mg dose; improvements were maintained through week 13
 - Was generally well tolerated. Many commonly reported TEAEs were consistent with known on-target effects of OX2R agonists
- The results of Vibrance-1 support the continued development of alixorexton as a treatment for NT1 in the ongoing Brilliance phase 3 studies (NCT07455383; NCT07540897)

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