Effects of Alixorexton on Patient-Reported Disease Severity, Cognitive Functioning, and Fatigue in Patients With Narcolepsy Type 1: Results From the Phase 2 Vibrance-1 Study

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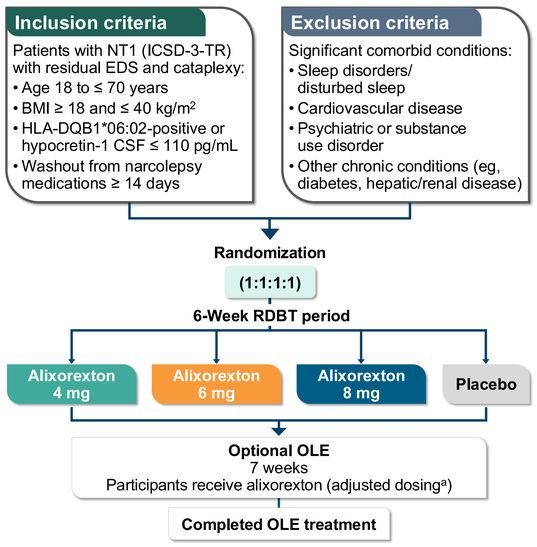
Introduction

- NT1 is characterized by EDS, cataplexy, sleep hallucinations, sleep paralysis, and disrupted nighttime sleep[1,2]
- Cognitive impairment and fatigue are clinically significant symptoms of NT1 that are recognized in the International Classification of Sleep Disorders diagnostic criteria[3-6]
- The pathophysiology of NT1 involves loss of orexin neurons, which project to brain regions that affect wakefulness, arousal, and cognition[3]
- Alixorexton (ALKS 2680) is a highly potent, oral, selective OX2R agonist under development as a treatment for narcolepsy and IH[7,8]
- Alixorexton achieved clinically meaningful and statistically significant improvements in the MWT (primary endpoint) and ESS (key secondary endpoint), and resulted in clinically meaningful reductions in WCR (key secondary endpoint) at the end of the 6-week treatment period in participants with NT1 in the phase 2 Vibrance-1 study (NCT06358950)
- Here we report the effects of alixorexton on disease severity, cognition, and fatigue in participants in Vibrance-1

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**)
- Exploratory assessments included disease severity, cognition, and fatigue
  - The NSS-CT is a 15-item self-administered questionnaire (score: 0-57) that assesses the severity and consequences of the 5 major narcolepsy symptoms (daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and disturbed nighttime sleep) over the past 7 days
  - The BC-CCI is a 6-item screening tool that assesses cognitive impairment as perceived by the patient over the past week. The BC-CCI-E includes 3 additional items that assess the impact of cognitive impairment on quality of life
  - The PROMIS-Fatigue 6a is a 6-item questionnaire designed to assess a patient's fatigue over the past 7 days
  - The PGI-S for Cognition and PGI-S for Fatigue are single items that ask patients to rate the severity of their cognitive impairment or fatigue, respectively, over the past 7 days
- In this presentation, participants are shown throughout the OLE by their original RDBT period randomization assignment

Figure 1. Study design



[a]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE.

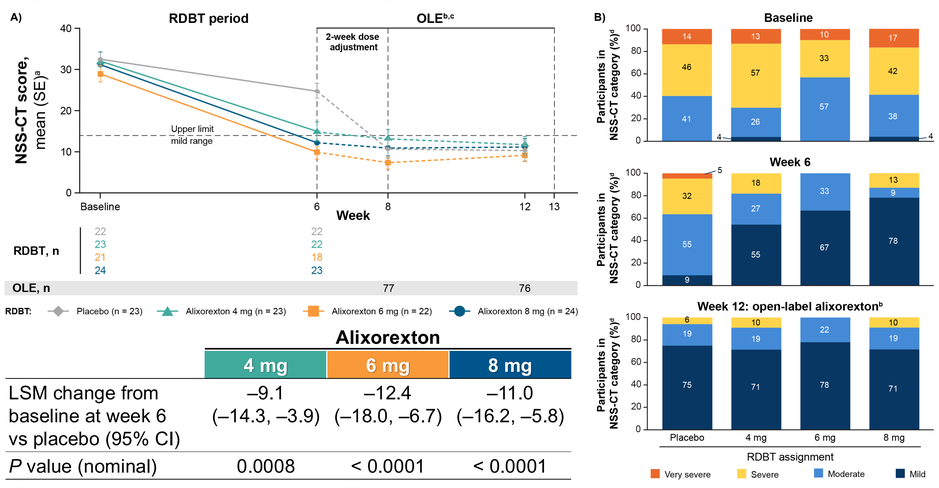
Results

- Overall, 92 participants were randomly assigned to treatment (placebo: 23; alixorexton 4 mg: 23; alixorexton 6 mg: 22, alixorexton 8 mg: 24)
- Participants had a mean age of 33.5 years, most (62%) were female, over one-third (38%) were white, and average BMI was 28.4 kg/m²

Narcolepsy symptom severity

- Alixorexton significantly reduced disease severity versus placebo at week 6 (nominal $P < 0.001$ for all comparisons), and effects were maintained through week 13 (**Figure 2A**)
  - Mean total NSS-CT scores decreased from baseline to week 6, with most participants falling within the mild disease range (< 14) at all alixorexton dose groups; the LSM difference in the change from baseline to week 6 in the alixorexton-treated groups versus placebo surpassed the 8-point MCID for this scale[9,10]
  - Most participants (55% to 78%) who received alixorexton rated their disease severity as mild at week 6, compared with 4% or less at baseline (**Figure 2B**)

Figure 2. NSS-CT A) score change and B) categorical change



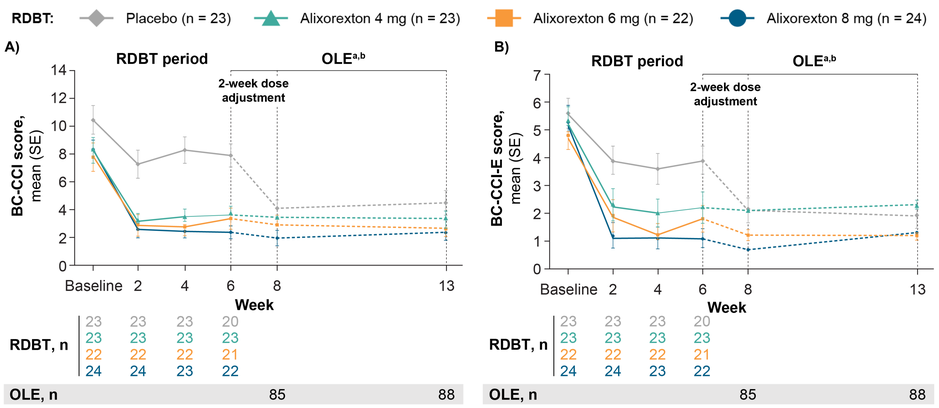
	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–9.1 (–14.3, –3.9)	–12.4 (–18.0, –6.7)	–11.0 (–16.2, –5.8)
P value (nominal)	0.0008	< 0.0001	< 0.0001

[a]The dashed horizontal line indicates upper limit for an NSS-CT score to correspond to mild severity. [b]All 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. [c]Dashed 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). [d]NSS-CT score ranges for each severity category are mild (0-14), moderate (15-28), severe (29-42), and very severe (43-57).

Cognition

- Alixorexton significantly reduced severity and impact of cognitive impairment versus placebo at week 6 (nominal $P < 0.01$ for all comparisons), and effects were maintained through week 13 (**Figure 3A**, **Figure 3B**)
  - At week 6, 90% of participants treated with alixorexton had no or minimal cognitive impairment (BC-CCI score ≤ 4)
  - At week 6, alixorexton significantly reduced the impact of cognitive impairment on quality of life (**Figure 3B**)
- Most participants treated with alixorexton reported no or mild cognitive impairment on the PGI-S for Cognition at weeks 6 and 13 (**Figure 4**)

Figure 3. A) BC-CCI: Severity of cognitive symptoms (6 items) and B) BC-CCI-E: Impact of cognitive symptoms (3 items)

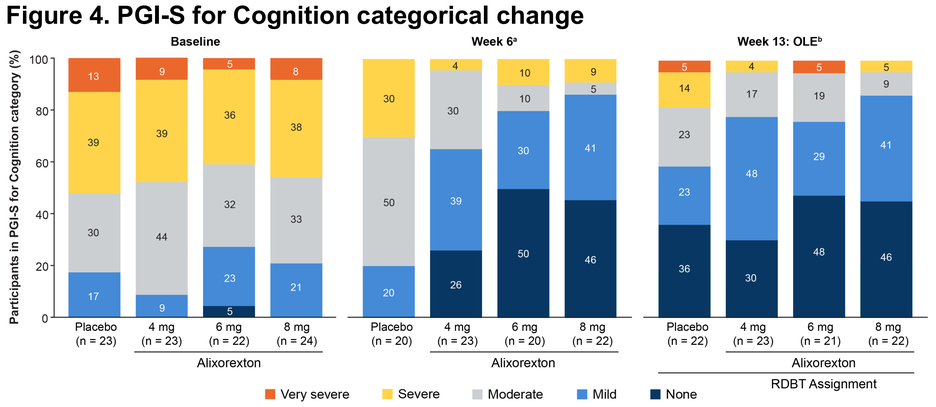


	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–3.5 (–5.1, –1.9)	–3.7 (–5.4, –2.1)	–4.8 (–6.4, –3.2)
P value (nominal)	< 0.0001	< 0.0001	< 0.0001

	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–1.7 (–2.8, –0.6)	–1.9 (–3.0, –0.8)	–2.7 (–3.8, –1.6)
P value (nominal)	0.0034	0.001	< 0.0001

[a]All 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. [b]Dashed 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).

Figure 4. PGI-S for Cognition categorical change

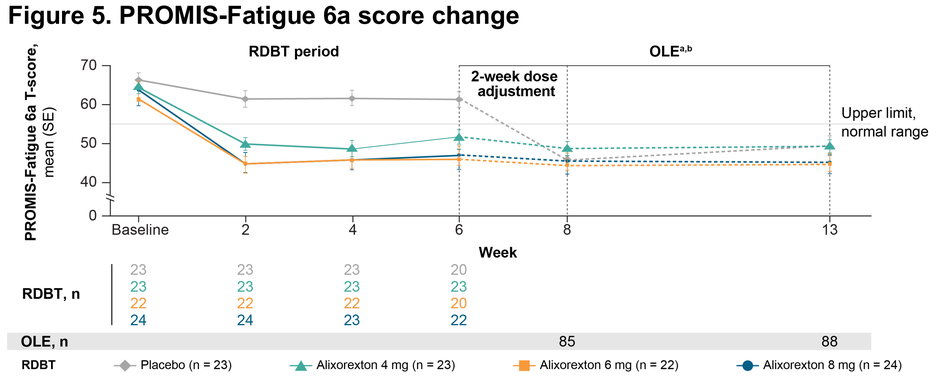


[a]At week 6, all doses of alixorexton were significantly different from placebo ($P = 0.0015$ for the 4 mg dose, $P = 0.0004$ for the 6 mg dose, and $P < 0.0001$ for the 8 mg dose, all nominal). [b]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment.

Fatigue

- Alixorexton significantly reduced fatigue at week 6 (nominal $P < 0.01$ for all comparisons), and effects were maintained through week 13 (**Figure 5**)
  - At week 6, mean PROMIS-Fatigue 6a T-scores reached normative levels (T-score ≤ 55)
- Most participants treated with alixorexton reported no or mild fatigue on the PGI-S for Fatigue at weeks 6 and 13 (**Figure 6**)

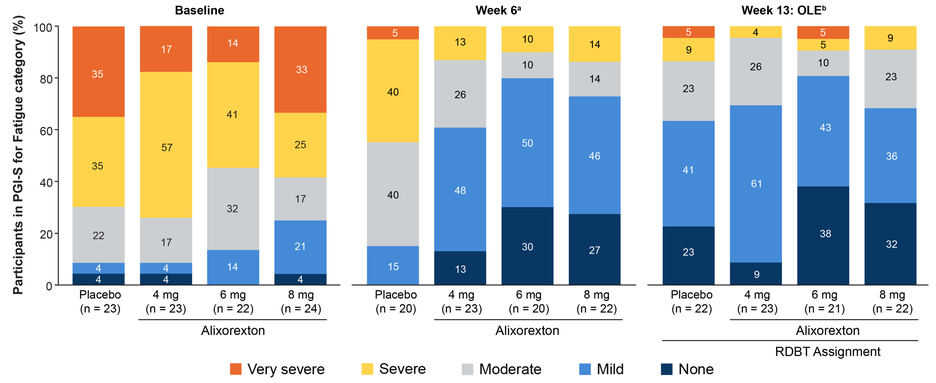
Figure 5. PROMIS-Fatigue 6a score change



	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–8.7 (–14.1, –3.3)	–12.4 (–17.9, –6.8)	–12.9 (–18.3, –7.5)
P value (nominal)	0.0018	< 0.0001	< 0.0001

[a]All 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. [b]Dashed 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).

Figure 6. PGI-S for Fatigue categorical change



[a]At week 6, all doses were significantly different from placebo ($P = 0.0019$ for the 4 mg dose, $P = 0.0003$ for the 6 mg dose, and $P = 0.0005$ for the 8 mg dose, all nominal). [b]All 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.

Conclusions

- Alixorexton demonstrated statistically significant (analyses for exploratory endpoints were unadjusted for multiplicity) and clinically meaningful improvements from baseline on established measures evaluating severity of participant-reported narcolepsy symptoms, cognitive impairment, and fatigue through 13 weeks of treatment
  - Most participants treated with alixorexton reported no or mild cognitive impairment and fatigue at the end of the OLE period
- 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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Abbreviations
BC-CCI, British Columbia Cognitive Complaints Inventory; BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; BMI, body mass index; CI, confidence interval; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ICSD-3-TR, International Classification of Sleep Disorders, Third Edition, Text Revision; IH, idiopathic hypersomnia; LSM, least-square means; MCID, minimal clinically important difference; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; NT1, narcolepsy type 1; OLE, open-label extension; OX2R, orexin 2 receptor; PGI-S, Patient Global Impression Scale-Severity; PROMIS, Patient-Reported Outcomes Measurement Information System; RDBT, randomized double-blind treatment; SD, standard deviation; SE, standard error; WCR, weekly cataplexy rate.

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