Alixorexton Improved Patient-Reported Disease Severity, Cognitive Functioning, and Fatigue in Patients With Narcolepsy Type 1 in the Vibrance-1 Study

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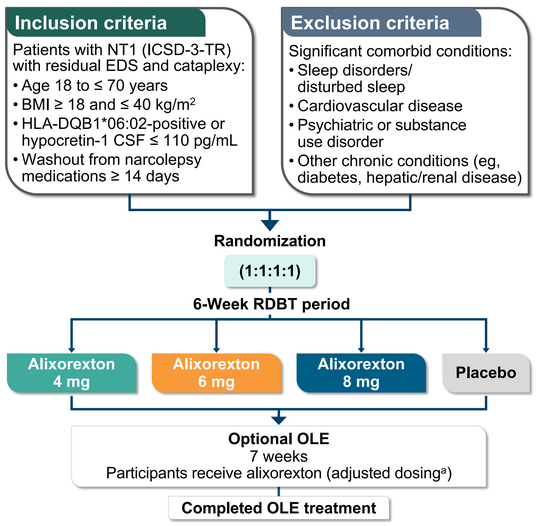
Introduction

- Narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness (EDS), cataplexy, sleep hallucinations, sleep paralysis, and disrupted nighttime sleep[1,2]
- 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 orexin 2 receptor agonist under development as a treatment for narcolepsy and idiopathic hypersomnia[7,8]
- Alixorexton achieved clinically meaningful and statistically significant improvements in the Maintenance of Wakefulness Test (MWT; primary endpoint) and Epworth Sleepiness Scale (ESS; key secondary endpoint), and resulted in clinically meaningful reductions in weekly cataplexy rate (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 Narcolepsy Severity Scale for Clinical Trials (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 British Columbia Cognitive Complaints Inventory (BC-CCI) is a 6-item screening tool that assesses cognitive impairment as perceived by the patient over the past week. The BC-CCI-Expanded (BC-CCI-E) includes 3 additional items that assess the impact of cognitive impairment on quality of life
  - The Patient Reported Outcomes Measurement Information System® Item Bank v1.0 - Fatigue - Short Form 6a (PROMIS-Fatigue) is a 6-item questionnaire designed to assess a patient's fatigue over the past 7 days
  - The Patient Global Impression Scale-Severity (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 open-label extension (OLE) by their original randomized double-blind treatment (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.
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.

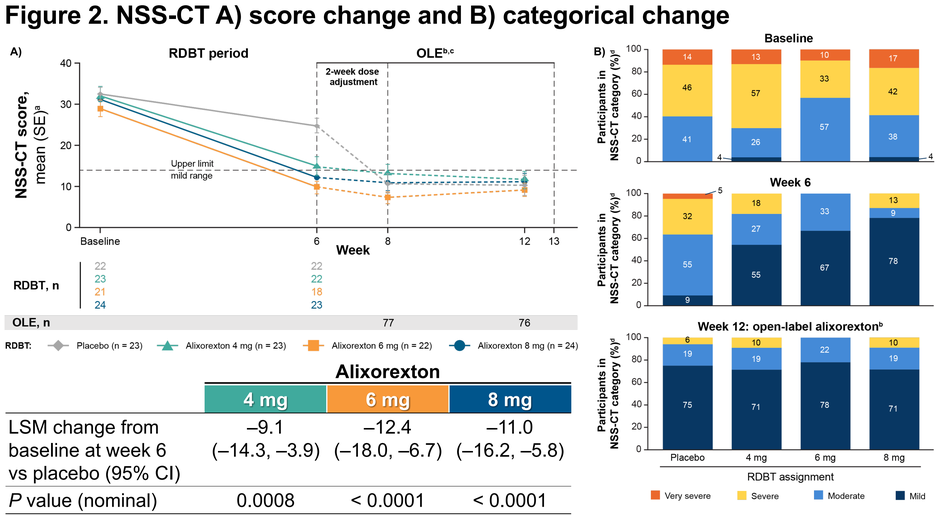
Results

- 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 body mass index 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 least-square means (LSM) difference in the change from baseline to week 6 in the alixorexton-treated groups versus placebo surpassed the 8-point minimal clinically important difference 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



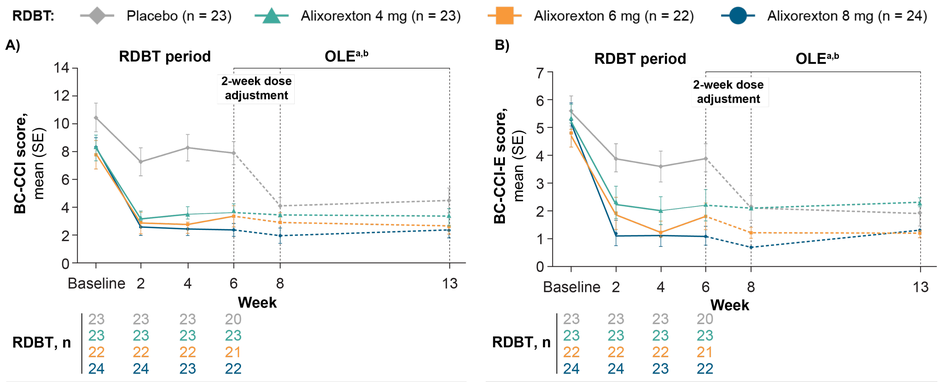
	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–9.1 (–14.3, –3.9)	–12.4 (–18.0, –6.7)	–11.0 (–16.2, –5.8)
P value (nominal)	0.0008	< 0.0001	< 0.0001

[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).
CI, confidence interval; LSM, least-square means; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; OLE, open-label extension; RDBT, randomized double-blind treatment; SE, standard error.

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)

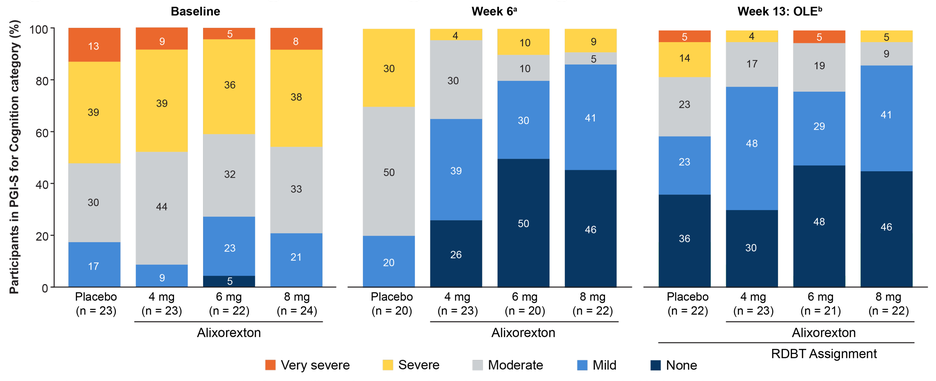


	Alixorexton		
	4 mg	6 mg	8 mg
LSM change from baseline at week 6 vs placebo (95% CI)	–3.5 (–5.1, –1.9)	–3.7 (–5.4, –2.1)	–4.8 (–6.4, –3.2)
P value (nominal)	< 0.0001	< 0.0001	< 0.0001

	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).
BC-CCI, British Columbia Cognitive Complaints Inventory; BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; CI, confidence interval; LSM, least-square means; OLE, open-label extension; RDBT, randomized double-blind treatment; SE, standard error.

Figure 4. PGI-S for Cognition categorical change

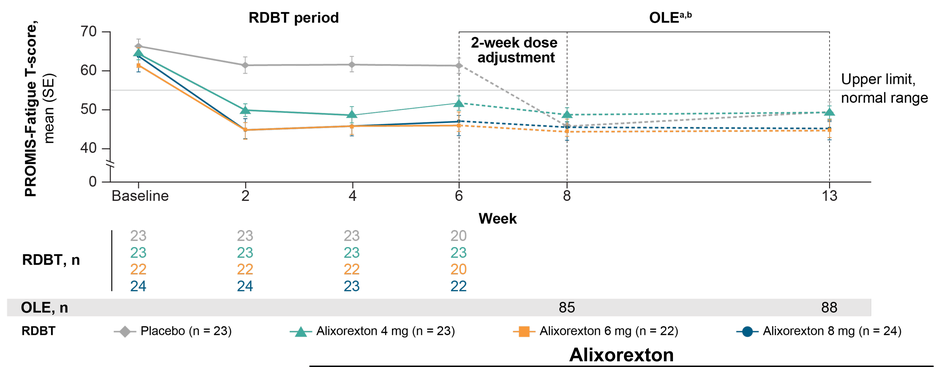


[a]At week 6, all doses of alixorexton were significantly different from placebo ($P = 0.0015$ for the 4 mg dose, $P = 0.0004$ for the 6 mg dose, and $P < 0.0001$ for the 8 mg dose, all nominal). [b]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment.
OLE, open-label extension; PGI-S, Patient Global Impression Scale-Severity; RDBT, randomized double-blind treatment.

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 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**)

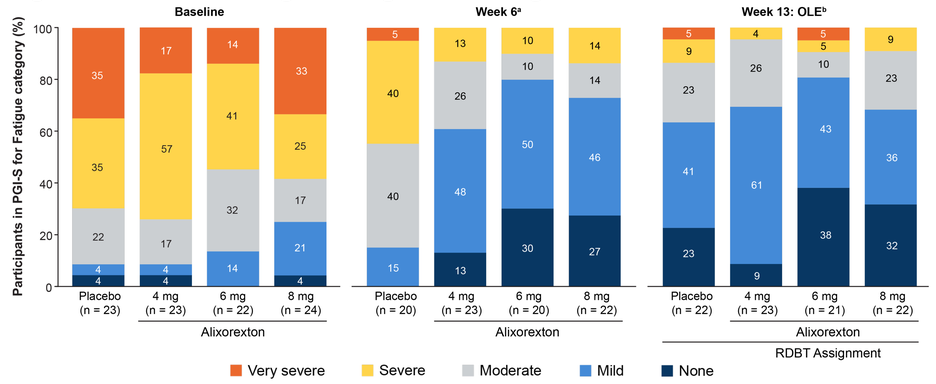
Figure 5. PROMIS-Fatigue score change



	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).
CI, confidence interval; LSM, least-square means; OLE, open-label extension; PROMIS-Fatigue, Patient Reported Outcomes Measurement Information System® Item Bank v1.0 - Fatigue - Short Form 6a; RDBT, randomized double-blind treatment; SE, standard error.

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.
OLE, open-label extension; PGI-S, Patient Global Impression Scale-Severity; RDBT, randomized double-blind treatment.

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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