Orexin 2 Receptor Agonists as a Potential Therapeutic Approach to the Treatment of Sleep-Wake Disturbance, Fatigue, and Cognitive Deficit in Neuropsychiatric Disease

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Introduction

- Orexin neuropeptides regulate sleep-wake behavior and stabilize wakefulness through activation of downstream arousal neurocircuitry, including monaminergic and cholinergic systems[1,2]
- Orexins signal through two receptors, orexin 1 receptor and orexin 2 receptor (OX2R), with converging evidence indicating a predominant role for OX2R signaling in maintaining wakefullness and stabilizing sleep-wake transitions[3-5]
- OX2R agonists have the potential to address symptoms of hypersomnolence, excessive fatigue, cognitive impairment, and depressed mood in neuropsychiatric disorders[6-8]
- The orexin system regulates attention, cognition, and memory, key functions affected in attention-deficit/hyperactivity disorder (ADHD). It may also contribute to fatigue and sleep disturbances in multiple sclerosis (MS) and Parkinson disease (PD)[9-12]
- ALKS 7290 and ALKS 4510 are potent, highly selective OX2R agonists with unique profiles that make them suitable for investigation as potential treatments in these diseases (**Table 1**). Here we present preclinical data evaluating ALKS 7290
- Alixorexton is a potent, highly selective OX2R agonist that is under development as a treatment for narcolepsy and idiopathic hypersomnia (IH) (**Table 1**) and has improved sleep-wake disturbance, fatigue, and cognitive impairment in patients with these disorders in clinical trials. Here we present an overview of key clinical trial data supporting the continued evaluation of alixorexton in phase 2 and 3 trials, and show the impact of OX2R agonism on cognition and fatigue in narcolepsy
- The biological rationale and data presented here will be used as a foundation for development plans for OX2R agonists in neuropsychiatric disorders, where there is a significant unmet need for adequate treatment

Table 1. OX2R agonist pipeline

OX2R agonist	Therapy area	Clinical trial stage
Alixorexton	NT1 and NT2	Phase 3
	IH	Phase 2
ALKS 7290	ADHD	Phase 1
ALKS 4510	Neurodegenerative disorders	Phase 1

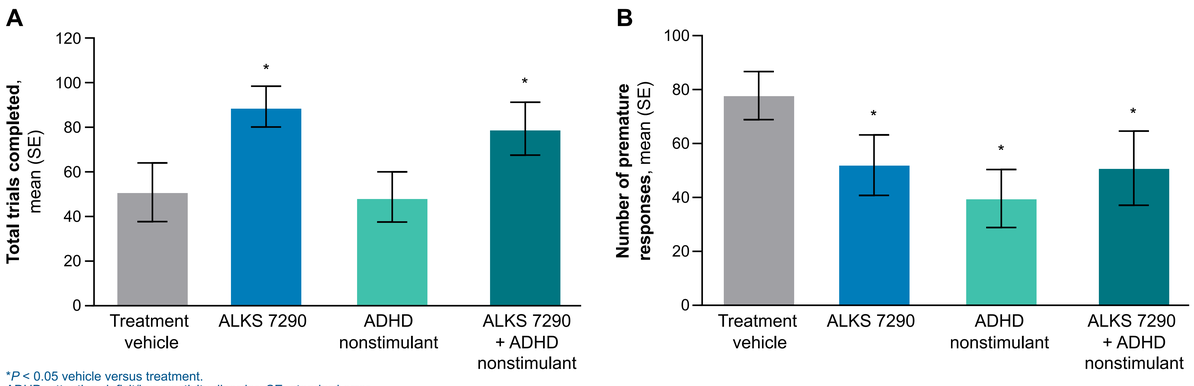
ADHD, attention-deficit/hyperactivity disorder; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OX2R, orexin 2 receptor.

OX2R agonists in ADHD and neurodegenerative disorders

ADHD

- ADHD is a neurological condition characterized by persistent difficulty in maintaining attention, frequently accompanied by hyperactive and impulsive behavior[13]
- Despite availability of stimulant and nonstimulant treatment options, there is still a considerable unmet need in this population[13]
- ALKS 7290 is an investigational OX2R agonist in development for the treatment of ADHD
- The 5-choice serial reaction time task is a preclinical measure of attention, task engagement, and impulse control with high clinical translation. In the task, an animal model (rats) must repeatedly attend and respond to a brief light in 1 of 5 locations to earn a reward[14,15]
- To test attention and task engagement, the intertrial time was shortened to challenge attentional capacity. To test impulse control, the intertrial time was lengthened to challenge impulsive responding. Across both studies, rats were grouped based on performance tertile with “low performer” representing the lowest tertile performance and “high impulsive” representing the highest tertile performance, allowing a mostly homogenous phenotype to be studied
  - Treatment with ALKS 7290 improved task performance by increasing the total trials completed in a subgroup of "low performer" rats (**Figure 1A**)
  - Treatment with ALKS 7290 decreased impulsive responding in a subgroup of "high impulsive" rats (**Figure 1B**)
- A phase 1 study is ongoing with single- and multiple-ascending dose cohorts of healthy volunteers
- The phase 1b portion evaluating safety, tolerability, and efficacy in participants with ADHD is also ongoing

Figure 1. Impact of ALKS 7290 in a preclinical model on A) task engagement and B) impulse control on the 5-choice serial reaction time task



*P < 0.05 vehicle versus treatment.
ADHD, attention-deficit/hyperactivity disorder; SE, standard error.

Fatigue in neurodegenerative disorders

- Sleep disruption and fatigue are common and distinct burdensome symptoms affecting most patients with MS and PD[10-12, 16,17]
- The role of the orexinergic system in sleep deprivation and fatigue in MS and PD provides a solid foundation for exploring the use of OX2R agonists in the treatment of fatigue associated with MS and PD[10-12]
- Preclinical data indicate that activation of OX2R improves fatigue-related behaviors, including enhancing effortful motivation and sustained attention (Alkermes data on file)
- ALKS 4510 is an investigational OX2R agonist in development for the treatment of fatigue associated with MS and PD, with the potential to expand development to additional indications in the future
- ALKS 4510 is being evaluated in a phase 1 dose escalation study in healthy volunteers, with single- and multiple-ascending dose cohorts

Alixorexton in narcolepsy and IH

- In a phase 1b study (ISRCTN98204977), single doses of alixorexton demonstrated clinically meaningful improvements in wakefulness in participants with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and IH, establishing the basis for alixorexton as a potential therapeutic approach for patients with narcolepsy and IH

NT1

- The Vibrance-1 phase 2 study (NCT06358950) showed improvement in wakefulness (**Figure 2A**, **Figure 2B**) and cataplexy in NT1 (see poster #T60)
  - Alixorexton was generally well tolerated
  - Alixorexton led to improvements in participant-reported outcome measures of cognition and fatigue, indicating the potential utility of orexin agonists beyond wakefulness (**Figure 2C** and **Figure 2D**; see poster #T59)
- The Brilliance phase 3 studies in NT1 are ongoing with once-daily and split dosing (NCT07455383; NCT07540897)

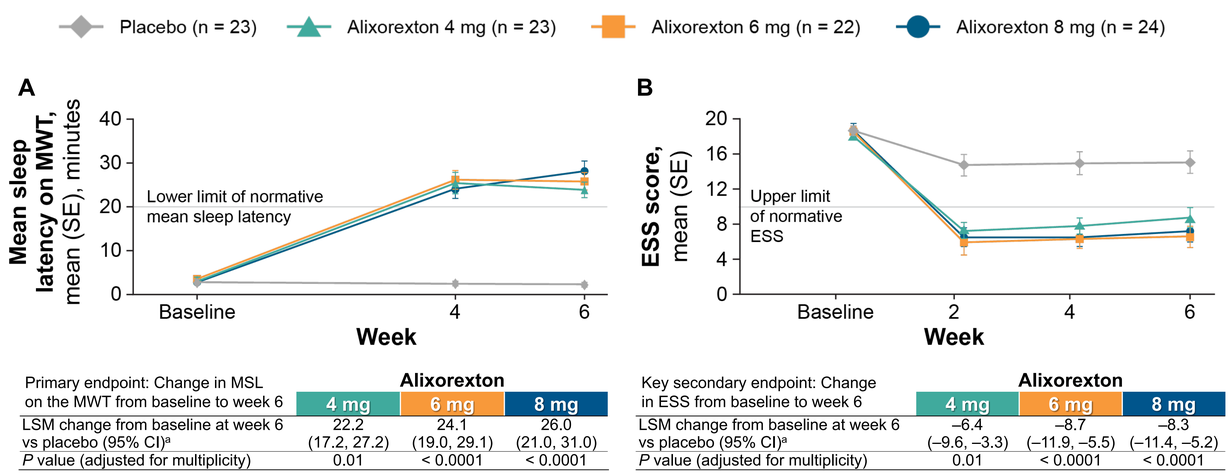
NT2

- Alixorexton was the first OX2R agonist to show clinically meaningful improvements in wakefulness and excessive daytime sleepiness in participants with NT2 in the Vibrance-2 phase 2 study (NCT06555783), demonstrating its utility in a clinical population without orexin deficiency
  - Alixorexton was generally well tolerated
- The Brilliance phase 3 study in NT2 is ongoing with once-daily and split dosing (NCT07502443)

IH

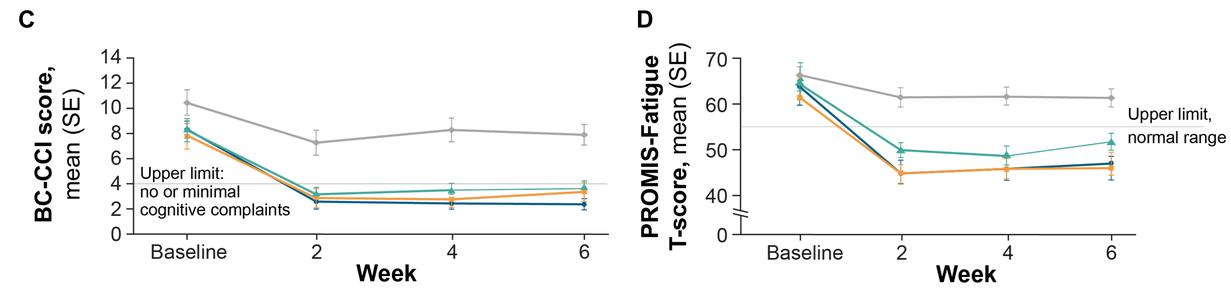
- The Vibrance-3 phase 2 study (NCT06843590) to evaluate safety and efficacy in participants with IH is ongoing with once-daily and split dosing

Figure 2. Alixorexton treatment effect on A) the primary endpoint of mean sleep latency (Maintenance of Wakefulness Test), B) a key secondary endpoint, wakefulness (Epworth Sleepiness Scale), and participant-reported C) severity of cognitive symptoms (British Columbia Cognitive Complaints Inventory), and D) fatigue (PROMIS® Item Bank v1.0 – Fatigue - Short Form 6a) in participants with NT1 in Vibrance-1



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

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



	Alixorexton 4 mg	Alixorexton 6 mg	Alixorexton 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	Alixorexton 6 mg	Alixorexton 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]Missing data were imputed using multiple imputation.
BC-CCI, British Columbia Cognitive Complaints Inventory; CI, confidence interval; ESS, Epworth Sleepiness Scale; LSM, least-square means; MSL, mean sleep latency; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; PROMIS-Fatigue, PROMIS® Item Bank v1.0 – Fatigue - Short Form 6a; SE, standard error.

Conclusions

- Given the role of the orexinergic system in cognitive impairment, sleep disturbance, and fatigue, and the effects of other OX2R agonists on these symptoms in other disorders, we are evaluating OX2R agonists in ADHD, neurodegenerative disorders, narcolepsy, and IH
- ALKS 7290 is in an ongoing phase 1 clinical study of healthy volunteers and a phase 1b study to evaluate safety, tolerability, and efficacy in adults with ADHD
- ALKS 4510 is being developed to treat fatigue associated with MS and PD and is currently being evaluated in a phase 1 clinical study in healthy volunteers, with plans for a phase 2 study to initiate later this year
- The efficacy of alixorexton has been established in the Vibrance-1 and Vibrance-2 phase 2 studies in participants with NT1 and NT2, respectively; the Vibrance-3 phase 2 trial in participants with IH is ongoing. Alixorexton is further being evaluated in the Brilliance program, comprised of 3 global, pivotal phase 3 studies, currently enrolling participants with NT1 and NT2
- OX2R agonists are a new investigational treatment class with the potential to advance standard of care and address unmet needs across central disorders of hypersomnolence and neuropsychiatric diseases that cause sleep-wake disturbances, cognitive impairment, or fatigue

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Disclosures
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Abbreviations
ADHD, attention-deficit/hyperactivity disorder; BC-CCI, British Columbia Cognitive Complaints Inventory; CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; LSM, least-square means; MS, multiple sclerosis; MSL, mean sleep latency; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OX2R, orexin 2 receptor; PD, Parkinson disease; PROMIS-Fatigue, PROMIS® Item Bank v1.0 – Fatigue - Short Form 6a; SE, standard error; US, United States.

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