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

Poster No. 71

David T. Plante,[1] Andrew J. Cutler,[2,3] Julie Brooks,[4] Ishani Landry,[4] Bhaskar Rege,[4] Julie Himes,[4] Craig Hopkinson,[4] and Emmanuel Mignot[5]

[1]University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI; [2]Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY; [3]Neuroscience Education Institute, Lakewood Ranch, FL; [4]Alkermes, Inc., Waltham, MA; [5]Stanford Center for Sleep Sciences and Medicine, Stanford University School of Medicine, Stanford, CA

Introduction

- Orexin neuropeptides regulate sleep-wake behavior and stabilize wakefulness through activation of downstream arousal neurocircuitry, including monoaminergic 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 wakefulness 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 that are affected in individuals with attention-deficit/hyperactivity disorder (ADHD). The orexin system may also contribute to fatigue associated with multiple sclerosis (MS) and Parkinson's disease (PD)[9-12]
- 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 participants with these disorders in clinical trials
- ALKS 7290 and ALKS 4510 are potent, highly selective OX2R agonists with unique profiles that make them suitable for investigation as potential treatments for ADHD and fatigue associated with neurodegenerative disorders, respectively (**Table 1**)
- Here, we present preclinical data evaluating ALKS 7290 and clinical data on alixorexton, supporting continued evaluation in phase 2 and 3 trials
- The biological rationale and data presented here will be used as a foundation for development plans for OX2R agonists in neuropsychiatric disorders

Table 1. OX2R agonist pipeline

OX2R agonist	Therapeutic area	Clinical trial stage
Alixorexton	NT1 and NT2	Phase 3
	IH	Phase 2
ALKS 7290	ADHD	Phase 2
ALKS 4510	Fatigue associated with neurodegenerative disorders	Phase 1

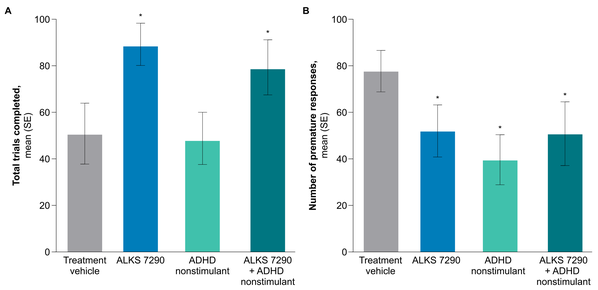
ADHD, attention-deficit/hyperactivity disorder; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OX2R, orexin 2 receptor.

OX2R agonists in ADHD and neurodegenerative disorders

ADHD

- ADHD is a neurological condition characterized by persistent difficulty in maintaining attention and is 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 (rat) 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 homogeneous 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 2 study evaluating the preliminary efficacy, safety, and tolerability of ALKS 7290 in participants with ADHD is ongoing (NCT07755410)

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



Panel A experiments were conducted in "low performer" rats. Panel B experiments were conducted in "high impulsive" rats.
*$P < 0.05$ versus vehicle.
ADHD, attention-deficit/hyperactivity disorder; SE, standard error.

Fatigue in neurodegenerative disorders

- Sleep disruption and fatigue are common and distinct burdensome symptoms affecting most individuals with MS and PD[10-12,16,17]
- 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

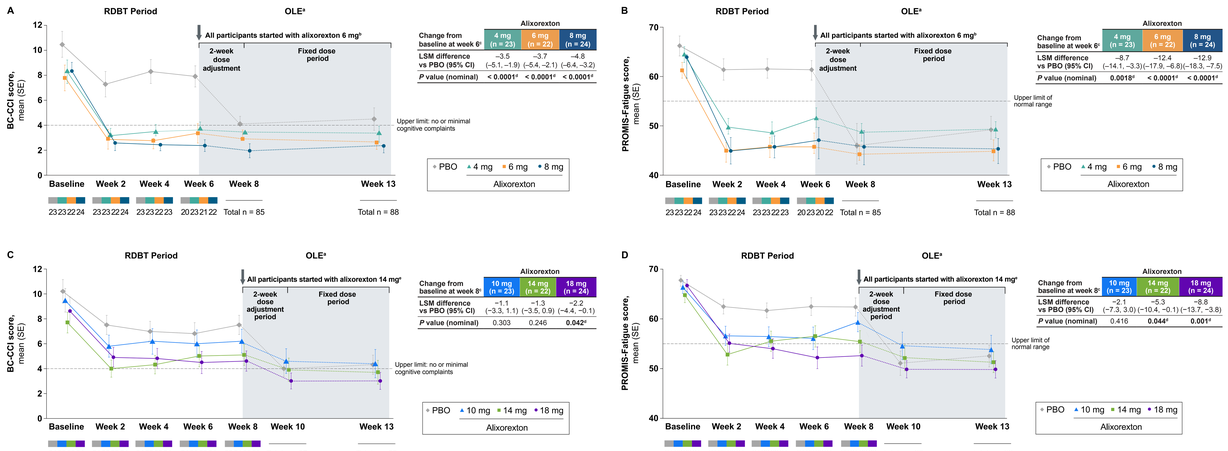
Alixorexton in narcolepsy and IH

- In a phase 1 study, single doses of alixorexton demonstrated clinically meaningful and statistically significant 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 participants with narcolepsy and IH

NT1

- Alixorexton showed clinically meaningful and statistically significant improvements from baseline in wakefulness (mean sleep latency [MSL] on the Maintenance of Wakefulness Test [MWT]), excessive daytime sleepiness (EDS; mean Epworth Sleepiness Scale [ESS] score), and cataplexy at week 6 in participants with NT1 in the Vibrance-1 phase 2 study (NCT06358950)[18]
- Alixorexton led to improvements in exploratory participant-reported outcome measures of cognition and fatigue, indicating the potential utility of orexin agonists beyond wakefulness (**Figures 2A** and **2B**, respectively); see poster no.152 for more detailed information
- Most TEAEs during the RDBT period and OLE were mild to moderate, and no serious TEAEs were reported during the study
- TEAEs occurring in ≥10% of participants treated with alixorexton in the RDBT period included pollakiuria, insomnia, salivary hypersecretion, micturition urgency, and vision blurred
- The Brilliance phase 3 studies in NT1 are ongoing with once-daily and split dosing (NCT07455383; NCT07540897)

Figure 2. Alixorexton treatment effect on severity of cognitive symptoms (BC-CCI) and fatigue (PROMIS-Fatigue) in participants with NT1 in Vibrance-1 (A and B, respectively) and NT2 in Vibrance-2 (C and D, respectively)



[a]Groups are shown by their RDBT randomization assignment through the OLE. [b]All participants in the OLE period started with alixorexton 6 mg. Dose adjustment was possible during the first 2 weeks of the optional OLE at the discretion of the investigator. [c]Cognition and fatigue data were exploratory endpoints in the Vibrance-1 and -2 studies, and were not included in the multiplicity control procedure used for primary and key secondary endpoints. [d]Statistically significant, unadjusted for multiplicity. [e]All participants in the OLE period started with alixorexton 14 mg. Dose adjustment was possible during the first 2 weeks of the optional OLE at the discretion of the investigator.
BC-CCI, British Columbia Cognitive Complaints Inventory; CI, confidence interval; LSM, least-squares mean; OLE, open-label extension; PBO, placebo; PROMIS-Fatigue, Patient Reported Outcomes Measurement Information System® Item Bank v1.0-Fatigue-Short Form 6a; RDBT, randomized double-blind treatment; SE, standard error.

NT2

- Alixorexton was the first oral OX2R agonist to show clinically meaningful and statistically significant improvements from baseline in wakefulness (MSL score on the MWT) and EDS (mean ESS score) at week 8 in participants with NT2 in a robust phase 2 study (Vibrance-2; NCT06555783), demonstrating its potential utility in a clinical population without orexin deficiency[19]
- Alixorexton led to improvements in exploratory participant-reported outcome measures of cognition and fatigue, indicating the potential utility of orexin agonists beyond wakefulness and EDS (**Figures 2C** and **2D**, respectively)
- Most TEAEs during the RDBT period and OLE were mild to moderate, and no serious TEAEs were reported during the study
- TEAEs occurring in ≥10% of participants treated with alixorexton in the RDBT period included pollakiuria, micturition urgency, insomnia, dizziness, and headache
- 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

Conclusions

- Given the role of the orexinergic system in cognitive impairment, sleep disturbance, and fatigue, as well as the effects of other investigational OX2R agonists on these symptoms in other disorders, we are evaluating OX2R agonists in ADHD, neurodegenerative disorders, narcolepsy, and IH
- In adults with ADHD, ALKS 7290 is being evaluated in a phase 2 study for efficacy, safety, and tolerability
- 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 2a study to initiate later this year
- Alixorexton has been evaluated 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, comprising 3 global 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 disturbance, cognitive impairment, or fatigue

Acknowledgments
The authors thank the Alkermes Neurobiology Team and all participants and study staff in the Vibrance phase 2 and Brilliance phase 3 studies. These studies were funded by Alkermes, Inc. Medical writing support was provided by Sarika Pathak Sharma, PhD, and Caroline Leitschuh, PhD, of Oxford PharmaGenesis Inc., Wilmington, DE, USA, and was funded by Alkermes, Inc., Waltham, MA, USA.

Disclosures
DTP participated in advisory boards for Aditum Bio LLC, Alkermes, Inc., Contessa, Eisai, Harmony Biosciences, Jazz Pharmaceuticals, Lundbeck, Takeda, and Teva. **AJC** has acted as consultant for Acadia, Anavex Life Sciences, Autobahn Therapeutics, Biogen, Biohaven, Boehringer Ingelheim, Bril Biosciences, Cerevel, Delpor, Evolution Research Group, J&J Innovative Medicine, Jazz Pharma, Karuna, LivaNova, Luye Pharma, MapLight Therapeutics, MedAvante-ProPhase, Mentavi, Neumora, Neuroscience Education Institute, NeuroSigma, PaxMedica, Relmada, Sage Therapeutics, Thynk, and Vistagen Therapeutics; has acted as consultant for and received speaker/promotional honoraria from AbbVie, Alfasigma, Alkermes, Axsome, Bristol Myers Squibb, Corium, Intra-Cellular Therapies, J&J, Lundbeck, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris Pharma, and Vanda Pharmaceuticals; has acted as consultant for and holds stock options in 4M Therapeutics; and has served on a data safety monitoring board for Alar Pharma, COMPASS Pathways, Freedom Biosciences, and Pain Therapeutics. **JB**, **IL**, **BR**, **JH**, and **CH** are employees and shareholders of Alkermes. **EM** received research funding from Avadel, Alkermes, Inc., Eisai, Jazz Pharmaceuticals, Takeda Pharmaceuticals, and Vanda.

References
1. Bassetti CLA et al. *Nat Rev Neurol*. 2019;15(9):519-39. 2. Nepovimova E et al. *Med Res Rev*. 2019;39(3):961-75. 3. Mieda M et al. *Front Endocrinol (Lausanne)*. 2013;4:57. 4. Pizza F et al. *J Sleep Res*. 2022;31(4):e13665. 5. Yamamoto H et al. *PLoS One*. 2022;17(7):e0271901. 6. Wang Y et al. *Front Neurosci*. 2025;19:1638270. 7. Jacobson LH et al. *J Intern Med*. 2022;291(5):533-56. 8. Katzman MA, Katzman MP. *Brain Sci*. 2022;12(2):150. 9. Knez R et al. *Neuropsychiatr Dis Treat*. 2022;18:2683-702. 10. Bhattarai JJ et al. *Mult Scler J Exp Transl Clin*. 2023;9(3):20552173231194352. 11. Schütz L et al. *J Parkinsons Dis*. 2022;12(7):2029-58. 12. Wang Q et al. *Front Aging Neurosci*. 2021;13:713201. 13. Brown TE et al. *Prim Care Companion CNS Disord*. 2019;21(3). 14. Higgins GA, Silenieks LB. *Curr Protoc Pharmacol*. 2017;78:5.49.1-5.49.34. 15. Alkermes, Inc; PLC presentation. Presented October 9, 2024. 16. Maestri M et al. *Sleep Breath*. 2020;24(2):413-24. 17. Suh S et al. *J Psychosom Res*. 2024;178:111606. 18. Plazzi G et al. *Lancet Neurol*. 2026. Published online August 24, 2026. doi:10.1016/S1474-4422(26)00278-4. 19. Bogan RK et al. Presentation. SLEEP; June 14-17, 2026.

Scan QR code to download posters

Poster no.152

This poster