



Alkermes Announces Positive Topline Results From Phase 1b Study of ALKS 2680 Demonstrating Improved Wakefulness in Patients With Narcolepsy Type 2 and Idiopathic Hypersomnia

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—Orexin 2 Receptor Agonist ALKS 2680 Demonstrated Clinically Meaningful and Statistically Significant Improvements from Baseline in Mean Sleep Latency Compared to Placebo at All Doses Tested in Both Narcolepsy Type 2 and Idiopathic Hypersomnia —

—ALKS 2680 Was Generally Well Tolerated at All Doses Tested —

—Dose-Dependent Effects and Pharmacodynamic Profile Support Advancement Into Planned Phase 2 Study —

DUBLIN, April 9, 2024 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced positive topline results from the narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH) cohorts of a phase 1b, proof-of-concept study evaluating ALKS 2680, the company's novel, investigational, oral orexin 2 receptor (OX2R) agonist in development as a once-daily treatment for narcolepsy. ALKS 2680 data demonstrated clinically meaningful and statistically significant improvements from baseline in mean sleep latency on the Maintenance of Wakefulness Test (MWT) compared to placebo at all doses tested. ALKS 2680 was generally well tolerated in both patient populations at all doses tested.

The phase 1b NT2 (n=9) and IH (n=8) study cohorts evaluated the safety, tolerability, pharmacokinetics and pharmacodynamics of ALKS 2680 via once-daily, single, oral administration. Participants were randomized to a four-way crossover study in which each participant received 5 mg, 12 mg and 25 mg of ALKS 2680, and placebo, with washout periods between each treatment. Topline results from each cohort are as follows:

Narcolepsy Type 2:

- In the nine patients with NT2, treatment with ALKS 2680 demonstrated improved wakefulness compared to placebo at all doses tested, with a clear dose response. Prior to treatment with ALKS 2680, these patients had baseline sleep latencies ranging from 3 to 33 minutes, with a mean sleep latency of 14 minutes at baseline. Treatment with ALKS 2680 resulted in statistically significant and clinically meaningful improvements in sleep latency in these patients with NT2, with a mean change from baseline versus placebo of 12 minutes at the 5 mg dose ($p < 0.05$), 19 minutes at the 12 mg dose ($p < 0.001$), and 21 minutes at the 25 mg dose ($p < 0.001$) (least squares mean difference). Placebo treatment in this cohort resulted in no change in mean sleep latency. At the 12 mg and 25 mg doses, the observed mean MWT scores over an eight-hour period post-dose were within the reported normal range for healthy individuals.¹
- ALKS 2680 was generally well tolerated across all doses tested in participants with NT2. All treatment-emergent adverse events (TEAEs) were transient and self-resolving. TEAEs were mild in severity, with the exception of one moderate case of pollakiuria at the highest dose (25 mg). AEs observed in >1 participant with NT2 and deemed to be related to study drug were pollakiuria, insomnia and dizziness. One mild, transient occurrence of photophobia was reported in a single patient at the 25 mg dose, which self-resolved within two hours of onset.
- There were no serious AEs or AEs leading to discontinuation in patients with NT2. Additionally, there were no clinically meaningful, treatment-emergent changes in hepatic and renal parameters, vital signs, or electrocardiogram (ECG) parameters.
- The company plans to initiate a phase 2 study in patients with NT2 in the second half of 2024.

Idiopathic Hypersomnia:

- In the eight patients with IH, treatment with ALKS 2680 demonstrated improved wakefulness compared to placebo at all doses tested, with a clear dose response. Prior to treatment with ALKS 2680, these patients had baseline sleep latencies ranging from 6 to 34 minutes, with a mean sleep latency of 23 minutes at baseline. Treatment with ALKS 2680 resulted in statistically significant and clinically meaningful improvements in sleep latency in these patients with IH, with a mean change from baseline versus placebo of 8 minutes at the 5 mg dose ($p < 0.05$), 11 minutes at the 12 mg dose ($p < 0.01$), and 18 minutes at the 25 mg dose ($p < 0.001$) (least squares mean difference). Placebo treatment in this cohort resulted in a two-minute reduction in mean sleep latency. At the 12 mg and 25 mg doses, the observed mean MWT scores over an eight-hour period post-dose were within the reported normal range for healthy individuals.¹
- ALKS 2680 was generally well tolerated across all doses tested in participants with IH. All TEAEs were transient and self-resolving. TEAEs were mild in severity, with the exception of one moderate case of pollakiuria at the highest dose (25 mg). AEs observed in >1 participant and deemed to be related to study drug were pollakiuria, insomnia and dizziness. One mild, transient occurrence of visual disturbance was reported in a single patient at the 25 mg dose, which self-resolved approximately one hour after onset.
- There were no serious AEs or AEs leading to discontinuation. Additionally, there were no clinically meaningful, treatment-

emergent changes in hepatic and renal parameters, vital signs, or ECG parameters.

"The magnitude and durability of effect of ALKS 2680 seen in this proof-of-concept study in patients with narcolepsy type 2 and idiopathic hypersomnia is exciting. These data support further clinical evaluation of ALKS 2680 and demonstrate that orexin 2 receptor agonists such as ALKS 2680 may have utility in treating sleep disorders in patients without known orexin deficiency," said Ron Grunstein, M.D., Ph.D., Head of Sleep and Circadian Research at the Woolcock Institute of Medical Research. "New treatment options are needed, and orexin agonists have the potential to transform the current treatment landscape for people living with narcolepsy."

"We're pleased to share these topline results in patients with narcolepsy type 2 and idiopathic hypersomnia, which build upon our previously disclosed phase 1b data in narcolepsy type 1. These data further validate our hypothesis that an orexin agonist with appropriate pharmaceutical properties has potential to provide significant clinical benefits for both narcolepsy type 1 and type 2 patient populations," said Craig Hopkinson, M.D., Chief Medical Officer and Executive Vice President of Research & Development at Alkermes. "With these data now in hand, we are moving quickly to select doses for a phase 2 study in narcolepsy type 2, which we plan to initiate in the second half of this year."

Alkermes expects to submit results from this phase 1b, proof-of-concept study to a peer-reviewed journal for publication and to present additional ALKS 2680 study results at upcoming scientific meetings.

About the ALKS 2680 Phase 1 Study

The phase 1 study for ALKS 2680 included single-ascending dose and multiple-ascending dose evaluations in healthy volunteers, and double-blind, cross-over treatment in patients with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH).

In the healthy volunteer phase of the study, each cohort included eight participants, six of whom were randomized to receive ALKS 2680 and two of whom received placebo. In the single-dose portion, ALKS 2680 was dosed from 1 mg to 50 mg. In the multiple-dose portion, participants received single daily doses of ALKS 2680 ranging from 3 mg to 25 mg strengths for up to 10 days. The objectives of this part of the study were to assess ALKS 2680's safety, tolerability, pharmacokinetics and pharmacodynamics.

The phase 1b proof-of-concept part of the study enrolled patients with NT1 (n=10), NT2 (n=9) or IH (n=8). Following an initial two-week washout period of existing medications, patients received single doses of three active dose levels of ALKS 2680 (1 mg, 3 mg and 8 mg for NT1; 5 mg, 12 mg and 25 mg for NT2 and IH) and placebo in a randomized sequence in a four-way crossover design, with washout periods between each treatment in the sequence. The objectives were to assess safety and tolerability, and changes from baseline in average sleep latency, as measured through the Maintenance of Wakefulness Test (MWT) at each cross-over, along with plasma PK, biomarkers such as quantitative electroencephalogram (qEEG) and event-related potential (ERP), and a cognitive test, the Sustained Attention to Response Task (SART).

About ALKS 2680

ALKS 2680 is a novel, investigational, oral, selective orexin 2 receptor (OX2R) agonist in development as a once-daily treatment for narcolepsy. Orexin neuropeptides are important regulators of the sleep/wake cycle through OX2R activation, and loss of orexinergic neurons in the brain is associated with excessive daytime sleepiness and cataplexy in narcolepsy.² ALKS 2680 was designed to address the underlying pathology of narcolepsy with the goal of improving duration of wakefulness and providing cataplexy control. Once-daily oral administration of ALKS 2680 was evaluated in a phase 1 study in healthy volunteers and people living with narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia.

About Alkermes plc

Alkermes plc is a global biopharmaceutical company that seeks to develop innovative medicines in the field of neuroscience. The company has a portfolio of proprietary commercial products for the treatment of alcohol dependence, opioid dependence, schizophrenia and bipolar I disorder, and a pipeline of clinical and preclinical candidates in development for neurological disorders. Headquartered in Dublin, Ireland, Alkermes has a research and development center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

Note Regarding Forward-Looking Statements

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: the potential therapeutic and commercial value of ALKS 2680; and the company's expectations regarding plans and timelines for further clinical development activities for ALKS 2680, including the phase 2 study and presentation of additional data from the phase 1 study. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether ALKS 2680 could be shown to be ineffective or unsafe; whether preclinical and initial clinical results for ALKS 2680 will be predictive of results of further clinical studies or real-world results; potential changes in the cost, scope and duration of the ALKS 2680 development program; whether future clinical trials or future stages of ongoing clinical trials for ALKS 2680 will be initiated or completed on time or at all; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2023 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

¹ Krahn LE, Arand DL, Avidan AY, et al. Recommended protocols for the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test in adults: guidance from the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2021;17(12):2489–2498.


² Nagahara T, Saitoh T, Kutsumura N, Irukayama-Tomobe Y, Ogawa Y, Kuroda D, Gouda H, Kumagai H, Fujii H, Yanagisawa M, Nagase H. Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists. *J Med Chem*. 2015 Oct 22;58(20):7931-7. doi: 10.1021/acs.jmedchem.5b00988. Epub 2015 Aug 26. PMID: 26267383.

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