



Alkermes Presents First Clinical Data for Orexin 2 Receptor Agonist ALKS 2680 at World Sleep Congress

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- *Initial ALKS 2680 Data Demonstrated Dose-Dependent, Significantly Improved Sleep Latency Compared to Placebo in Narcolepsy Type 1* —
 - *ALKS 2680 Was Generally Well Tolerated at All Doses Tested* —
 - *Pharmacokinetic Profile of ALKS 2680 Supports Once-Daily Dosing and Mimics the Natural Sleep/Wake Cycle* —
 - *Consistent, Dose-Dependent Effects Enable Dose Selection for Evaluation in Planned Phase 2 Study* —

DUBLIN, Oct. 23, 2023 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced preliminary results, including initial proof-of-concept data, from a phase 1 study evaluating ALKS 2680, the company's novel, investigational orexin 2 receptor (OX2R) agonist in development for the treatment of narcolepsy. The ongoing phase 1 study is evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of ALKS 2680 in healthy volunteers and patients with narcolepsy or idiopathic hypersomnia via once-daily, oral administration. Initial data from the single- and multiple-ascending dose evaluations in healthy volunteers and the first cohort of four patients with narcolepsy type 1 (NT1) will be presented today at the 2023 World Sleep Congress in Rio de Janeiro.

The patients with NT1 were randomized to a crossover study in which each of them received 1 mg, 3 mg and 8 mg of ALKS 2680, and placebo, with washout periods between each treatment. Single administration of each dose strength of ALKS 2680 achieved statistically significant, clinically meaningful improvements compared to placebo in wakefulness, as measured by the maintenance of wakefulness test (MWT).

In the four patients with NT1, treatment with ALKS 2680 demonstrated improved sleep latency compared to placebo at all doses tested, with a clear dose response. Following treatment with ALKS 2680, mean sleep latency in patients improved by 18 minutes, 30 minutes and 37 minutes from mean pre-treatment baseline sleep latency of three minutes at the 1 mg, 3 mg and 8 mg doses, respectively (least squares mean). Placebo treatment resulted in a one-minute reduction in mean sleep latency. The differences between ALKS 2680 and placebo were statistically significant for all doses: 1 mg ($p<0.01$), 3 mg ($p<0.001$), and 8 mg ($p<0.001$).

Treatment with ALKS 2680 resulted in clinically meaningful improvements in MWT from baseline at all doses tested. At the 8 mg dose of ALKS 2680, patients maintained wakefulness for the full 40-minute MWT duration, up to 10 hours post-dose. MWT scores at 3 mg were comparable to the 8 mg scores for the first 6 hours post-dose, and treatment with both the 1 mg and 3 mg doses of ALKS 2680 resulted in improved MWT scores up to 8 hours post-dose.

ALKS 2680 was generally well tolerated across all doses tested in the patients with NT1. Drug-related adverse events (AEs) were seen only at the 8 mg dose and were mild in severity. The AEs observed in >1 participant and deemed to be treatment-emergent at the 8 mg dose were insomnia ($n=3$), pollakiuria (urinary urgency or frequency) ($n=2$) and salivary hypersecretion ($n=2$). 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 electrocardiogram (ECG) parameters.

"The early proof-of-concept and safety data we've seen in this ongoing phase 1 study of ALKS 2680 in both healthy volunteers and four patients with narcolepsy type 1 are compelling. These data support further evaluation of ALKS 2680 as a potential treatment for narcolepsy," said Brendon Yee, Ph.D., Professor and Respiratory and Sleep Physician at the Woolcock Institute of Medical Research. "Orexin 2 receptor agonists such as ALKS 2680 represent an exciting new class of potential treatments for narcolepsy, with the opportunity to transform the treatment paradigm for people living with this disease."

In healthy volunteers, ALKS 2680 was evaluated at single- and multiple-ascending doses. In the single-dose evaluation, ALKS 2680 was dosed from 1 mg to 50 mg. In the multiple-dose evaluation, participants received single daily doses of ALKS 2680 at 3 mg, 8 mg, 15 mg and 25 mg strengths for up to 10 days. ALKS 2680 was generally well tolerated across all doses tested and the maximum tolerated dose was not reached. Most AEs were mild, transient, and resolved without intervention or treatment interruption. In the single-ascending dose evaluation, AEs observed in >1 participant and deemed related to study drug were dizziness, pollakiuria, nausea and blurred vision, and most occurred at or above the 15 mg dose level. In the multiple-ascending dose evaluation, AEs observed in >1 participant and deemed related to study drug were insomnia, dizziness, pollakiuria and visual disturbances described as blurred or distorted vision, and most occurred at or above the 8 mg dose. There were no safety signals identified in vital signs, laboratory parameters or ECGs.

In healthy volunteers, ALKS 2680 was observed to be centrally active and to have a pharmacokinetic and pharmacodynamic profile that supports once-daily, oral dosing.

"Narcolepsy is a serious, chronic, neurological disease that impairs regulation of the sleep-wake cycle and negatively impacts daily life. There is significant unmet need for people with narcolepsy, as no currently available treatments address the underlying biology of the disease: orexin deficiency or dysfunction," said Craig Hopkinson, M.D., Chief Medical Officer and Executive Vice President of Research & Development at Alkermes. "These initial data support our design rationale for ALKS 2680 as a highly potent, orally bioavailable, selective orexin 2 receptor agonist designed to address the underlying pathology of narcolepsy. The consistent and dose-dependent effects observed in the initial proof-of-concept data enable dose selection for evaluation in phase 2. We look forward to sharing additional updates from the phase 1 study, and plan to initiate our phase 2 study of ALKS 2680, in the first half of 2024."

About the ALKS 2680 Phase 1 Study

The phase 1 study for ALKS 2680 includes single-ascending dose and multiple-ascending dose evaluations in healthy volunteers, and a 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 at 3 mg, 8 mg, 15 mg and 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 is enrolling patients with NT1, NT2 or IH, with up to eight patients for each such indication. Following an initial two-week washout period of existing medications, patients receive single doses of three active dose levels of ALKS 2680 and placebo in a randomized sequence in a four-way crossover design, with washout periods between each treatment in the sequence. The primary objectives are to assess safety and tolerability, and changes from baseline in the average sleep latency 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). Data from the first four patients with NT1 will be presented at World Sleep Congress.

About ALKS 2680

ALKS 2680 is a novel, investigational, oral, selective orexin 2 receptor (OX2R) agonist in development for the treatment of 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.¹ 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 is currently being 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 fully-integrated, global biopharmaceutical company developing innovative medicines in the fields of neuroscience and oncology. The company has a portfolio of proprietary commercial products focused on alcohol dependence, opioid dependence, schizophrenia and bipolar I disorder, and a pipeline of product candidates in development for neurological disorders and cancer. Headquartered in Dublin, Ireland, Alkermes has a research and development (R&D) 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 for the treatment of narcolepsy; the company's expectations regarding plans and timelines for further clinical development activities for ALKS 2680, including dose selection, initiation of 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, 2022 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 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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