Alkermes Announces Publication of Phase 3 Data for ALKS 5461 for Adjunctive Treatment of Major Depressive Disorder in Molecular Psychiatry

October 29, 2018

-- ALKS 5461 Demonstrated Consistent Profile of Antidepressant Activity, Safety and Tolerability in Two Phase 3 Studies --

-- New Drug Application for ALKS 5461 Currently Under FDA Review With Target Action Date of Jan. 31, 2019 --

DUBLIN, Oct. 29, 2018 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced that *Molecular Psychiatry* has published phase 3 clinical data for ALKS 5461 (buprenorphine/samidorphan), a once-daily, oral investigational medicine that acts as an opioid system modulator and represents a novel mechanism of action for the adjunctive treatment of major depressive disorder (MDD) in patients with an inadequate response to standard antidepressant therapies. The *Molecular Psychiatry* publication includes comprehensive efficacy and safety results from FORWARD-4 (Study 205) and FORWARD-5 (Study 207), and a review of a pooled analysis of the two datasets. Collectively, ALKS 5461 demonstrated a consistent profile of antidepressant activity, safety and tolerability in the adjunctive treatment of MDD.

"Major depressive disorder is a leading contributor to the overall global burden of disease, affecting an estimated 16.2 million people in the U.S.[1] For those receiving treatment, approximately two-thirds do not respond to currently approved therapies, all of which are designed to work by primarily targeting the monoamine system[2]," said Maurizio Fava, M.D., Director of the Division of Clinical Research of the Massachusetts General Hospital (MGH) Research Institute and lead author of the publication. "New therapies with novel mechanisms of action are desperately needed to treat major depressive disorder. The endogenous opioid system is a fundamental regulator of mood and is thought to play a critical role in depression. These published data further demonstrate that an opioid system modulator may improve major depressive symptoms when added to standard treatments."

FORWARD-4 and FORWARD-5 were phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ALKS 5461 as an adjunctive treatment in patients with MDD who had experienced inadequate response to standard antidepressant therapies. Both studies utilized a sequential parallel-comparison design (SPCD), which includes two treatment stages and two randomizations in a single study to reduce the impact of placebo response commonly seen in psychiatric trials. SPCD builds on traditional placebo run-in designs, adding a randomly assigned active arm during the run-in phase to address treatment-related expectations and improve ascertainment of placebo non-response. The most common adverse events for ALKS 5461 in these studies included nausea, constipation, dizziness, vomiting, somnolence, fatigue and sedation. In these studies, ALKS 5461 showed low abuse potential and minimal evidence of dependence or opioid withdrawal as assessed by adverse events or the Clinical Opiate Withdrawal Scale (COWS).

"The peer-reviewed publication of these phase 3 results in *Molecular Psychiatry* presents an important opportunity to share with the clinical community the dataset supporting the efficacy and safety profile for ALKS 5461. ALKS 5461 represents a new mechanism of action for the adjunctive treatment of major depressive disorder, and its unique pharmacology targeting the endogenous opioid system may provide distinct clinical benefits for people with MDD who do not get adequate relief from first-line standard antidepressant therapy," said Craig Hopkinson, M.D., Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs at Alkermes. "These data reinforce the breadth of the ALKS 5461 clinical program and its consistent profile of antidepressant activity, safety and tolerability in the adjunctive treatment of MDD. We look forward to continuing to work with the FDA during its review of the ALKS 5461 regulatory submission, with the goal of helping to bring this potential new medicine to patients."

The New Drug Application (NDA) for ALKS 5461 is currently under U.S. Food and Drug Administration (FDA) review, with a FDA Advisory Committee meeting scheduled on Nov. 1, 2018 and a target action date of Jan. 31, 2019. The NDA filing for ALKS 5461 is based on results from a clinical efficacy and safety package with data from more than 30 clinical trials and more than 1,500 patients with MDD.

About ALKS 5461

ALKS 5461 is a proprietary, investigational, once-daily oral medicine that acts as an opioid system modulator and represents a novel mechanism of action for the adjunctive treatment of major depressive disorder (MDD) in patients with an inadequate response to standard antidepressant therapies. ALKS 5461 is a fixed-dose combination of buprenorphine, a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist, and samidorphan, a mu-opioid receptor antagonist.

About MDD

According to the *DSM-5*® (*Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*), major depressive disorder (MDD) is a condition in which patients exhibit depressive symptoms, such as a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and demonstrate impaired social, occupational, educational or other important functioning. An estimated 16.2 million people in the U.S. suffered from MDD in 2016,[1] the majority of whom may not adequately respond to initial antidepressant therapy.[2]

About Alkermes plc

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases. The company has a diversified commercial product portfolio and a substantial clinical pipeline of product candidates for chronic diseases that include schizophrenia, depression, addiction and multiple sclerosis. Headquartered in Dublin, Ireland, Alkermes plc has an 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: review and potential approval by the FDA of the ALKS 5461 NDA and the anticipated timing of such review and approval; and the potential therapeutic and commercial value of ALKS 5461. You are cautioned 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 the preclinical and clinical results of ALKS 5461 studies will meet the regulatory requirements for approval by the FDA; whether the FDA's bases for the rescinded Refusal to File letter for the ALKS 5461 NDA or other bases will cause the FDA to require more data or information prior to approval of ALKS 5461; whether ALKS 5461 will be approved by the FDA in a timely manner or at all; and those risks and uncertainties described under the heading "Risk Factors" in the company's most recent Annual Report on Form 10-K 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.

DSM-5® is a registered trademark of the American Psychiatric Association.

[1] National Institutes of Mental Health: Major Depression. Accessed on Oct. 29, 2018 from https://www.nimh.nih.gov/health/statistics/major-depression.shtml.

[2] Rush AJ et al (2007) *Am J. Psychiatry,* 163:11, pp. 1905-1917 (STAR*D Study).

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View original content to download multimedia:http://www.prnewswire.com/news-releases/alkermes-announces-publication-of-phase-3-data-for-alks-5461-for-adjunctive-treatment-of-major-depressive-disorder-in-molecular-psychiatry-300739455.html

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