Alkermes Announces Topline Results of FORWARD-3 and FORWARD-4, Two Phase 3 Studies of ALKS 5461 in Major Depressive Disorder

January 21, 2016

-- Neither Study Met Primary Endpoint; Additional Analyses of FORWARD-4 Provide Supportive Evidence of Efficacy --

-- Third Efficacy Study, FORWARD-5, Will Recruit Additional Patients; Data May Provide Regulatory Path Forward for ALKS 5461 --

DUBLIN--(BUSINESS WIRE)--Jan. 21, 2016-- Alkermes plc (NASDAQ: ALKS) today announced preliminary topline results from FORWARD-3 and FORWARD-4, the first two of three phase 3 efficacy studies to read out from the comprehensive FORWARD pivotal program for ALKS 5461, a once-daily, oral investigational medicine with a novel mechanism of action for the adjunctive treatment of major depressive disorder (MDD) in patients who have an inadequate response to standard therapies for clinical depression. Neither of the two studies met the prespecified primary efficacy endpoint, which compared ALKS 5461 to placebo on the change from baseline on the Montgomery–Åsberg Depression Rating Scale (MADRS).

FORWARD-4 tested two dose levels of ALKS 5461 (2mg/2mg and 0.5mg/0.5mg) compared to placebo. 385 patients entered the study. There was a clear trend toward efficacy with the 2mg/2mg dose of ALKS 5461 on the primary endpoint, and post hoc analyses achieved statistical significance for the entire 2mg/2mg dose group on the MADRS endpoint. Based on these analyses, Alkermes believes that FORWARD-4 provides supportive evidence of the efficacy of ALKS 5461 in the treatment of major depressive disorder.

FORWARD-3 tested ALKS 5461 (2mg/2mg) compared to placebo. 429 patients entered the study. Placebo response was greater than that observed in FORWARD-4 and no treatment effect of ALKS 5461 was observed. Negative trials due to significant placebo effect are not uncommon in the study of major depressive disorder.

FORWARD-5, the third pivotal efficacy study in the FORWARD program, is ongoing, testing two dose levels of ALKS 5461 (2mg/2mg and 1mg/1mg). FORWARD-5 shares common design and analysis features with FORWARD-4. Based on information gained from FORWARD-3 and FORWARD-4, patient enrollment in FORWARD-5 will be increased and the statistical analysis plan will be updated. Alkermes will provide an update later this quarter on the projected timing of completion of FORWARD-5.

In the case of a clear positive outcome for FORWARD-5, Alkermes believes that the evidence provided by it and the previously completed successful, randomized, placebo-controlled phase 2 study, together with supportive evidence from FORWARD-4, collectively could provide substantial evidence of efficacy for ALKS 5461 for the adjunctive treatment of MDD. In that case, Alkermes would request a meeting with the U.S. Food and Drug Administration's (FDA) Division of Psychiatric Products to discuss the regulatory path for this Fast Track designated medicine.

"We are gaining important insights as we proceed with the FORWARD program for ALKS 5461. The third pivotal efficacy study, FORWARD-5, is ongoing and we plan to adapt it to incorporate findings from FORWARD-3 and FORWARD-4," stated Elliot Ehrich, M.D., Chief Medical Officer of Alkermes. "Clinical trials of new medicines for the treatment of major depressive disorder are complicated by significant placebo response. We designed the FORWARD pivotal program to include three efficacy studies as we recognize that this is a challenging disease state where multiple clinical studies and expansive analyses are generally necessary to confirm the efficacy of a new medicine."

"We are steadfast in our commitment to developing new medicines for serious CNS conditions where there is a clear and compelling need for new treatment options for patients and their families," said Richard Pops, Chief Executive Officer of Alkermes. "Major depressive disorder is one of these conditions. We are building a large body of evidence supporting our belief in the clinical utility and the novel mechanism of action of ALKS 5461. We await the results of FORWARD-5 and will determine our next steps along the regulatory path with those results in hand."

In FORWARD-3, the most commonly reported adverse events were nausea, headache and fatigue, and in FORWARD-4 they were nausea, headache and dizziness. The safety and tolerability profile of ALKS 5461 was consistent with that reported for the phase 2 and FORWARD-1 studies.

About FORWARD-3 and FORWARD-4
FORWARD-3 and FORWARD-4 are phase 3, randomized, double-blind, multicenter, placebo-controlled studies that evaluated the safety, tolerability and efficacy of once-daily ALKS 5461 as adjunctive treatment in patients with MDD who had an inadequate response to a stable dose of either a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). The prespecified primary endpoint of both studies was the change from baseline in MADRS scores. All participants in the double-blind portion of the study were eligible to continue in an open-label phase and receive ALKS 5461 for an additional 12 months.

About the Phase 3 FORWARD Clinical Program
The FORWARD (**F**ocused **O**n **R**esults **W**ith **A** **R**ethinking of **D**epression) pivotal program for ALKS 5461 includes three core phase 3 efficacy studies, as well as additional supportive studies to evaluate the long-term safety, dosing, pharmacokinetic profile and human abuse potential of ALKS 5461. The primary efficacy endpoint for the three core efficacy studies is the change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) scores.

Further information about the FORWARD studies can be found at www.clinicaltrials.gov.

About ALKS 5461
ALKS 5461 is a proprietary, oral investigational medicine that acts as a balanced neuromodulator in the brain and represents a novel mechanism of action for treating MDD. ALKS 5461 consists of samidorphan and buprenorphine, and is designed to rebalance brain function that is dysregulated in the state of depression. In October 2013, the FDA granted Fast Track status for ALKS 5461 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressant therapies.

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 17 million people in the U.S. suffer from MDD in a given year,[1,2] the majority of whom may not adequately respond to initial antidepressant therapy.[3]

About Alkermes

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: the therapeutic value, development and regulatory plans, and commercial potential 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 projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether preclinical and clinical results for ALKS 5461 will be predictive of future clinical study results; whether future clinical trials for ALKS 5461 will be completed on time or at all; potential changes in cost, scope and duration of the ALKS 5461 clinical development program; whether ALKS 5461 could be shown ineffective or unsafe during clinical studies; whether the preclinical and clinical results of ALKS 5461 will meet the regulatory requirements for approval; whether regulatory submissions may occur or are submitted in a timely manner; and those risks described in the Alkermes plc Quarterly Report on Form 10-Q for the period ended Sept. 30, 2015 and Annual Report on Form 10-K for the fiscal year ended Dec. 31, 2014, and in other 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. The information contained in this press release is provided by the company as of the date hereof, and, except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking information contained in this press release.

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

[1] Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005 Jun; 62 (6): 617-27.

[2] U.S. Census.

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

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