Alkermes Presents Positive Results from Phase 2 Clinical Study of ALKS 5461 in Major Depressive Disorder at 53rd Annual NCDEU Meeting

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—Novel Mechanism Represents New Treatment Approach for Patients With Inadequate Response to Conventional Antidepressants —

HOLLYWOOD, Fla. & DUBLIN--(BUSINESS WIRE)--May. 31, 2013-- Alkermes plc (NASDAQ: ALKS) today announced the presentation of positive phase 2 data for ALKS 5461, a novel opioid modulator, in patients with major depressive disorder (MDD) and inadequate response to standard therapies. In the phase 2 study, ALKS 5461 met its primary endpoint, met key secondary endpoints and demonstrated significant reduction in depressive symptoms versus placebo. The study is being presented in an oral session at the 53rd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting in Hollywood, Fla., by Maurizio Fava, M.D., of Massachusetts General Hospital and Harvard Medical School.

“The magnitude of effect seen with ALKS 5461 in this study is highly significant. These results are very encouraging for ALKS 5461 as a potential new treatment approach, with substantial reductions in depressive symptoms demonstrated and rapid onset of action observed,” stated Maurizio Fava, M.D., Director of the Depression Clinical and Research Program at Massachusetts General Hospital and Slater Family Professor of Psychiatry at Harvard Medical School.

The phase 2 study of ALKS 5461 utilized a sequential parallel comparison design (SPCD), designed to reduce the impact of clinically meaningful response to treatment with placebo. The study included two four-week, randomized, double-blind stages run in sequence: an Initial Study Stage and a Successive Study Stage. The Successive Study Stage randomized only those patients who were non-responders to placebo in the Initial Study Stage. Both stages of the phase 2 study evaluated two doses of ALKS 5461, a lower dose and a higher dose. Overall, the combined analysis of both doses at both stages showed statistically significant efficacy on multiple endpoints compared to placebo. Overall, the lower dose showed greater efficacy than the higher dose and, as a result, will be the top end of the dose range employed in future studies. Results for the lower dose from the Successive Study Stage of the study included:

- ALKS 5461 significantly reduced Hamilton Depression Rating Scale (HAM-D17) scores from baseline (p=0.013), with a reduction of 5.3 points, compared to a reduction of 1.2 points in the placebo group at the end of the four-week treatment period. ALKS 5461 also significantly reduced Montgomery–Åsberg Depression Rating Scale (MADRS) scores from baseline (p=0.004), with a reduction of 8.7 points, compared to a reduction of 1.8 points in the placebo group at the end of the four-week treatment period.
- ALKS 5461 had an onset of effect, as measured by MADRS, evident after one week of treatment.

In the phase 2 results for the overall study population, including both the Initial Study Stage and the Successive Study Stage, patients who received either dose of ALKS 5461 for a treatment period of four weeks showed a significant reduction in depressive symptoms from baseline in HAM-D17 (p=0.026) and MADRS (p=0.004) scores, compared to placebo. The primary endpoint of the phase 2 study was the change from baseline in depressive symptoms over a four-week treatment period in the overall study population, as measured by HAM-D17, compared to placebo. Data from the study showed that ALKS 5461 was generally well tolerated. The most common adverse events observed in the study were nausea, headache and dizziness.

“ALKS 5461 reflects a new approach to the treatment of major depressive disorder based on modulation of the opioid system in the brain. With these compelling data in hand, we are planning to meet with the U.S. FDA as we work to advance ALKS 5461 to pivotal clinical development,” stated Elliot Ehrich, M.D., Chief Medical Officer of Alkermes. “ALKS 5461, one of several product candidates in our advancing clinical pipeline, is an excellent example of how Alkermes is leveraging our unique understanding of opioid biology and pharmacology to develop medications that address unmet medical needs for central nervous system disorders.”

Study Design

This phase 2, randomized, double-blind, multicenter, placebo-controlled study assessed the efficacy and safety of once-daily ALKS 5461 as adjunctive treatment in 142 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). Two doses of ALKS 5461 were evaluated, each with a 1:1 ratio of buprenorphine and ALKS 33 (lower dose of 2mg/2mg and higher dose of 8mg/8mg). The primary endpoint of the study was the change from baseline in depressive symptoms over a four-week treatment period, as measured by HAM-D17. Secondary endpoints included additional analyses of patient responses based on HAM-D17, MADRS and Clinical Global Impression – Severity Scale (CGI-S) scores.

The study utilized a sequential parallel comparison design (SPCD), a design developed ten years ago by Drs. Fava and Schoenfeld at Massachusetts General Hospital and now widely utilized in clinical trials. A SPCD trial involves two randomized, double-blind stages run in sequence. In the Initial Study Stage (stage 1), patients are randomized to either drug treatment or placebo. In the ALKS 5461 phase 2 study, the Initial Study Stage was a four-week treatment period. At the end of the Initial Study Stage, patients were reassigned treatment groups for the Successive Study Stage (stage 2), which in the ALKS 5461 phase 2 study was a second four-week treatment period. In the Successive Study Stage, patients who had been on drug in the Initial Study Stage were put on placebo. Patients who had been administered placebo in the Initial Study Stage were determined to be either responders, i.e., they responded positively to placebo treatment, or non-responders. Placebo responders were assigned to remain on placebo in the Successive Study Stage. Placebo non-responders were re-randomized to either placebo or drug treatment in the Successive Study Stage. SPCD

studies are particularly useful in studies of depression, anxiety and other difficult psychiatric diseases to reduce the impact of placebo effect on the assessment of treatment response.

About ALKS 5461

ALKS 5461 is a proprietary investigational medicine with a novel mechanism for the treatment of major depressive disorder (MDD). The mechanism of action for ALKS 5461 in the treatment of depressive symptoms is based on modulation of the opioid system in the brain, employing a balanced combination of agonism and antagonism of opioid receptors. ALKS 5461 consists of buprenorphine, a partial agonist, and ALKS 33, a potent mu-opioid antagonist, and is designed to be a once-daily, non-addictive medicine. Early clinical development of ALKS 5461 was funded through a grant from the National Institute on Drug Abuse (NIDA).

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 16.1 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 plc

Alkermes plc is a fully integrated, global biopharmaceutical company that applies its scientific expertise and proprietary technologies to develop innovative medicines that improve patient outcomes. The company has a diversified portfolio of more than 20 commercial drug products and a substantial clinical pipeline of product candidates that address central nervous system (CNS) disorders such as addiction, schizophrenia and depression. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and manufacturing facilities in Gainesville, Georgia and 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, including, but not limited to statements concerning: the therapeutic value of ALKS 5461; the clinical development of ALKS 5461, including meetings with regulatory authorities and the product's clinical development timeline; and the timing of the company's planned presentation of phase 2 data 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 the company will initiate a pivotal development program for ALKS 5461; 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; and those risks described in the Alkermes plc Annual Report on Form 10-K for the year ended March 31, 2013, and in other 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 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).

Source: Alkermes plc

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