Alkermes to Initiate New Clinical Study Evaluating ARISTADA® and INVEGA SUSTENNA® for the Treatment of Schizophrenia

October 26, 2017

— Phase 3b Study Will Assess Investigational Product Designed for Initiation Onto ARISTADA —

— Efficacy and Safety of Two-Month ARISTADA Compared to Market Leader INVEGA SUSTENNA Will Also be Evaluated —

DUBLIN--(BUSINESS WIRE)--Oct. 26, 2017-- Alkermes plc (NASDAQ: ALKS) today announced plans to initiate a phase 3b clinical study to evaluate the efficacy and safety of ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension and INVEGA SUSTENNA® (paliperidone palmitate) in patients experiencing an acute exacerbation of schizophrenia. Subjects in the ARISTADA treatment arm will receive Aripiprazole Lauroxil NanoCrystal® Dispersion (AL_{NCD}), a novel, investigational product designed for initiation onto ARISTADA, followed by the two-month dose of ARISTADA for a total of six treatment months. Alkermes recently submitted a New Drug Application (NDA) for AL_{NCD} to the U.S. Food and Drug Administration (FDA).

“This study evaluating ARISTADA alongside INVEGA SUSTENNA, a medicine which is recognized in the medical community as a highly effective therapeutic option for schizophrenia, will provide helpful insight into the utility of these treatment options,” said Elliot Ehrich, M.D., Executive Vice President, Research and Development of Alkermes. “The use of Aripiprazole Lauroxil NanoCrystal Dispersion to initiate onto two-month ARISTADA prior to hospital discharge represents an innovative approach to treating schizophrenia, and one we believe has the potential to significantly change the treatment paradigm.”

The prospective, randomized, multicenter, double-blind, phase 3b study announced today will evaluate the efficacy and safety of both ARISTADA and INVEGA SUSTENNA in approximately 180 subjects experiencing an acute exacerbation of schizophrenia. Patients will be randomized to either the ARISTADA treatment group (AL_{NCD} along with a single oral dose of 30 mg aripiprazole, followed by two-month ARISTADA) or the INVEGA SUSTENNA treatment group (starting dose followed by monthly INVEGA SUSTENNA) for a total of six treatment months. The primary efficacy endpoint of the study is the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4 within each treatment group. Secondary endpoints include the change in PANSS total score between treatment groups at Week 4 and the change from baseline in PANSS total score at the end of the six-month study. Alkermes expects to initiate this study in November 2017.

This phase 3b study follows the recent data presentation of Alkermes’ phase 4 clinical study at the 30 th Annual Psych Congress in September. The phase 4 open-label study showed that switching to treatment with ARISTADA was associated with statistically significant and clinically meaningful improvement in schizophrenia symptoms at the end of the six-month study in patients who had experienced inadequate response or intolerance to INVEGA SUSTENNA.

About Schizophrenia

Schizophrenia is a chronic, severe and disabling brain disorder. The disease is marked by positive symptoms (hallucinations and delusions) and negative symptoms (depression, blunted emotions and social withdrawal), as well as by disorganized thinking. An estimated 2.4 million American adults have schizophrenia,[1] with men and women affected equally.

About ARISTADA®

ARISTADA is an injectable atypical antipsychotic approved in four doses and three dosing durations for the treatment of schizophrenia (441 mg, 662 mg or 882 mg monthly, 882 mg once every six weeks, and 1064 mg once every two months). Once in the body, ARISTADA converts to aripiprazole. Oral aripiprazole should be administered for 21 consecutive days in conjunction with the first injection of ARISTADA. Alkermes has submitted a New Drug Application (NDA) for Aripiprazole Lauroxil NanoCrystal® Dispersion (AL_{NCD}), an investigational product designed for initiation onto ARISTADA, to the U.S. Food and Drug Administration (FDA). If approved, administration of AL_{NCD} in conjunction with a single oral dose of 30 mg aripiprazole will replace the need for three weeks of concomitant oral aripiprazole with the first dose of ARISTADA.

INDICATION and IMPORTANT SAFETY INFORMATION for ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

INDICATION

ARISTADA is indicated for the treatment of schizophrenia.

IMPORTANT SAFETY INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Reactions, Including Stroke: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, have been reported in placebo-controlled trials of elderly patients with dementia-related psychosis treated with risperidone, aripiprazole, and olanzapine. ARISTADA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including ARISTADA. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. Discontinue ARISTADA if clinically appropriate. TD may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.
- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Compulsive or uncontrollable urges to gamble have been reported with use of aripiprazole. Other compulsive urges less frequently reported include sexual urges, shopping, binge eating and other impulsive or compulsive behaviors which may result in harm for the patient and others if not recognized. Closely monitor patients and consider dose reduction or stopping ARISTADA if a patient develops such urges.

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension which can be associated with dizziness, lightheadedness, and tachycardia. Monitor heart rate and blood pressure, and warn patients with known cardiovascular or cerebrovascular disease and risk of dehydration and syncope.

Falls: Antipsychotics including ARISTADA may cause somnolence, postural hypotension or motor and sensory instability which may lead to falls and subsequent injury. Upon initiating treatment and recurrently, complete fall risk assessments as appropriate.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia should have frequent complete blood count (CBC) during the first few months of receiving ARISTADA. Consider discontinuation of ARISTADA at the first sign of a clinically significant decline in WBC count in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ARISTADA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC until recovery.

Seizures: ARISTADA should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ARISTADA may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain ARISTADA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use; use caution in patients at risk for aspiration pneumonia.

Concomitant Medication: Decreasing the ARISTADA dosage is recommended in patients taking strong CYP3A4 inhibitors and/or strong CYP2D6 inhibitors for longer than 2 weeks. Increasing the ARISTADA dosage from 441 mg to 662 mg is recommended in patients taking CYP3A4 inducers for longer than 2 weeks. No ARISTADA dosage changes are recommended for patients taking CYP450 modulators for less than 2 weeks.

Most Commonly Observed Adverse Reaction: The most common adverse reaction (≥5% incidence and at least twice the rate of placebo reported by patients treated with ARISTADA 441 mg and 882 mg monthly) was akathisia.

Injection-Site Reactions: Injection-site reactions were reported by 4%, 5%, and 2% of patients treated with 441 mg ARISTADA (monthly), 882 mg ARISTADA (monthly), and placebo, respectively. Most of these were injection-site pain and associated with the first injection and decreased with each subsequent injection. Other injection-site reactions (induration, swelling, and redness) occurred at less than 1%.

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider of a known or suspected pregnancy. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA during pregnancy. Aripiprazole is present in human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for ARISTADA and any potential adverse effects on the infant from ARISTADA or from the underlying maternal condition.

Please see FULL PRESCRIBING INFORMATION, including **Boxed Warning**, for ARISTADA.

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 potential therapeutic and commercial value of AL_{NCD} and ARISTADA for the treatment of schizophrenia; and the planned development activities for AL_{NCD} and ARISTADA. 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 the NDA for AL_{NCD} will be accepted and approved by the FDA; if approved, whether AL_{NCD} will be commercialized successfully; whether ARISTADA or AL_{NCD} could be shown ineffective or unsafe; 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, 2016 and Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017 and June 30, 2017 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]National Institutes of Health. *Schizophrenia*. Accessed Oct. 25, 2017 from https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=67.

View source version on businesswire.com: http://www.businesswire.com/news/home/20171026005713/en/

Source: Alkermes plc

Alkermes Contacts:
For Investors:
Eva Stroynowski, +1 781-609-6823
or
Sandy Coombs, +1 781-609-6377
or
For Media:
Lindsey Smith, +1 781-609-6231