Alkermes Announces Positive Topline Results From Innovative Study of ARISTADA® and INVEGA SUSTENNA® for the Treatment of Schizophrenia

April 9, 2019

-- Large, randomized ALPINE trial showed both long-acting injectable medications effectively controlled schizophrenia symptoms throughout six-month study --

-- ARISTADA demonstrated significant and similar efficacy to current market-leader INVEGA SUSTENNA, with differences in safety and tolerability parameters --

-- Data provide clinical evidence of efficacy, safety and tolerability of ARISTADA INITIO® and once-every-two-month ARISTADA dosing regimen, with favorable overall retention rate in study --

DUBLIN, April 9, 2019 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced positive topline results from ALPINE (**A**ripiprazole **L**auroxil and **P**aliperidone palmitate: **IN**itiation **E**ffectiveness), a first-of-its-kind, six-month study evaluating the efficacy, safety and tolerability of ARISTADA® (aripiprazole lauroxil) and INVEGA SUSTENNA® (paliperidone palmitate) when used to initiate patients experiencing an acute exacerbation of schizophrenia in the hospital and maintain treatment in an outpatient setting. Patients randomized to the ARISTADA treatment group were initiated using the ARISTADA INITIO® regimen* followed by ARISTADA (1064 mg) every two months. Patients randomized to the INVEGA SUSTENNA treatment group were initiated using a loading dose of INVEGA SUSTENNA (234 mg) followed by INVEGA SUSTENNA (156 mg) every month.

"The ALPINE study showed that both ARISTADA, given every two months, and INVEGA SUSTENNA, given every month, demonstrated statistically significant improvements from baseline in schizophrenia symptoms, and that the efficacy was similar for both medicines throughout the six-month study. This research provides evidence that these two long-acting medicines, each with their own distinct safety and tolerability profile, may be clinically useful in helping to bridge the critical transition between inpatient and outpatient settings of care," said Craig Hopkinson, M.D., Chief Medical Officer at Alkermes. "These data underscore that ARISTADA INITIO along with the two-month dose of ARISTADA together represent a novel approach to treatment initiation and a compelling clinical option for patients and healthcare professionals alike. The ALPINE study illustrates Alkermes' commitment to expanding the body of evidence for schizophrenia treatment and developing important medicines that help meet critical unmet needs in patient care."

The ALPINE study met its pre-specified primary endpoint, demonstrating that both ARISTADA and INVEGA SUSTENNA had statistically significant and clinically meaningful reductions in Positive and Negative Syndrome Scale (PANSS) total scores from baseline at Week 4 (ARISTADA group: -17.4 points, $p<0.001$; INVEGA SUSTENNA group: -20.1 points, $p<0.001$). Additionally, PANSS total scores continued to improve at Week 9 and Week 25, the study's pre-specified secondary endpoints (ARISTADA group: -19.8 points, $p<0.001$ at Week 9 and -23.3 points, $p<0.001$ at Week 25; INVEGA SUSTENNA group: -22.5 points, $p<0.001$ at Week 9 and -21.7 points, $p<0.001$ at Week 25). Improvements in PANSS total scores from baseline were similar and not statistically different between treatment groups at any assessment time point during the study.

The most common adverse events reported in the ARISTADA treatment group were injection site pain (17.2%), increase in weight (9.1%) and akathisia (9.1%). The most common adverse events reported in the INVEGA SUSTENNA treatment group were injection site pain (24.8%), increase in weight (16.8%) and akathisia (10.9%). Overall, 56.6% of patients in the ARISTADA treatment group and 42.6% of patients in the INVEGA SUSTENNA treatment group completed the six-month study.

"People living with schizophrenia face a complex treatment system and countless challenges that can disrupt continuity of care and make them vulnerable to relapse and re-hospitalization," said Dr. Jelena Kunovac, founder and president, Altea Research, and ALPINE study investigator. "The results from ALPINE validate the role that long-acting atypical antipsychotics can play in rapidly and effectively stabilizing patients in the hospital and supporting their continuity of care after discharge. The ability to start and stay on effective medication is essential to helping patients and caregivers achieve long-term treatment goals."

Alkermes expects to submit results from the ALPINE study to peer-reviewed journals for publication and present full study results, including efficacy, safety, tolerability and exploratory analyses, at upcoming scientific meetings.

ALPINE Study Design

ALPINE was a multicenter, randomized, double-blind, phase 3b study evaluating the efficacy, safety and tolerability of ARISTADA and INVEGA SUSTENNA in 200 subjects experiencing an acute exacerbation of schizophrenia. The study included a two-week inpatient phase, during which all subjects were initiated onto either ARISTADA or INVEGA SUSTENNA, followed by an outpatient phase for a total of six months. Patients randomized to the ARISTADA treatment group were initiated using the ARISTADA INITIO regimen—comprised of ARISTADA INITIO (675 mg) in combination with a single 30 mg oral dose of aripiprazole—on day 1, followed by ARISTADA (1064 mg) on day 8 and every two months thereafter. Patients randomized to the INVEGA SUSTENNA treatment group received an initiation dose of INVEGA SUSTENNA (234 mg) on day 1, followed by INVEGA SUSTENNA (156 mg) on day 8 and every month thereafter.

The study's pre-specified primary endpoint was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total scores at Week 4 within each treatment group. Pre-specified secondary endpoints included the change from baseline in PANSS total scores at Week 9 and Week 25 within each treatment group, as well as between treatment group comparisons at Week 4, Week 9 and Week 25. PANSS is a standard psychiatric scale used for measuring symptom severity in schizophrenia.

About Schizophrenia

Schizophrenia is a complex and often difficult-to-treat disease that affects more than 2.4 million people in the U.S.,[1] contributes to more than 800,000 hospital admissions each year[2] and results in an estimated $32-65 billion in treatment and other economic costs annually.[3] One study of adults hospitalized with schizophrenia found that approximately 40 percent did not receive any outpatient follow-up care within 30 days of discharge [4] and another found that among patients who are hospitalized and discharged, more than 15 percent are readmitted within 30 days.[5] Long-acting therapies for schizophrenia may help eliminate the burden of taking a daily oral antipsychotic and support medication adherence,[6] which is a key factor in risk of relapse.[7] However, despite research demonstrating the benefits of long-acting injectable antipsychotics (LAIs), including potential improvements in

symptoms,[6] only 11 percent of patients with schizophrenia in the U.S. are treated with LAIs.[8]

About ARISTADA INITIO®
ARISTADA INITIO, in combination with a single 30 mg dose of oral aripiprazole, is indicated for the initiation of ARISTADA when used for the treatment of schizophrenia in adults and can be used to initiate patients onto any dose of ARISTADA. The first ARISTADA dose may be administered on the same day as the ARISTADA INITIO regimen or up to 10 days thereafter.

About ARISTADA®
ARISTADA is an injectable atypical antipsychotic approved in the U.S. 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.

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

INDICATION

ARISTADA INITIO, in combination with oral aripiprazole, is indicated for the initiation of ARISTADA when used for the treatment of schizophrenia in adults.

ARISTADA is indicated for the treatment of schizophrenia in adults.

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 INITIO and ARISTADA are 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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

Potential for Dosing and Medication Errors: Medication errors, including substitution and dispensing errors, between ARISTADA INITIO and ARISTADA could occur. ARISTADA INITIO is intended for single administration in contrast to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex may occur with administration of antipsychotic drugs, including ARISTADA INITIO and 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 antipsychotics 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

aripiprazole 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 INITIO and 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 with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ARISTADA INITIO and/or ARISTADA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: Use with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ARISTADA INITIO and ARISTADA may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain therapy with ARISTADA INITIO and/or 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: ARISTADA INITIO is only available at a single strength as a single-dose pre-filled syringe, so dosage adjustments are not possible. Avoid use in patients who are known CYP2D6 poor metabolizers or taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers, antihypertensive drugs or benzodiazepines.

Depending on the ARISTADA dose, adjustments may be recommended if patients are 1) known as CYP2D6 poor metabolizers and/or 2) taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers for greater than 2 weeks. Avoid use of ARISTADA 662mg, 882mg, or 1064 mg for patients taking both strong CYP3A4 inhibitors and strong CYP2D6 Inhibitors. (See Table 4 in the ARISTADA full Prescribing Information)

Commonly Observed Adverse Reactions: In pharmacokinetic studies the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA**.** The most common adverse reaction (≥5% incidence and at least twice the rate of placebo reported by patients treated with ARISTADA 441mg and 882 mg monthly) was akathisia.

Injection-Site Reactions: In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injection site reactions with ARISTADA INITIO were similar to the incidence observed with ARISTADA. 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 INITIO and/or 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 INITIO and/or ARISTADA and any potential adverse effects on the infant from ARISTADA INITIO and/or ARISTADA or from the underlying maternal condition.

Please see full Prescribing Information, including Boxed Warning for ARISTADA INITIO and 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, multiple sclerosis and oncology. 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 LAIs, of ARISTADA, and of the ARISTADA INITIO regimen for initiation onto ARISTADA, for the treatment of schizophrenia; and timing and expectations regarding further reporting, and submission for publication, of the ALPINE study results. 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 results from the ALPINE study are predictive of real-world results, 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, 2018 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.

*The ARISTADA INITIO regimen is comprised of ARISTADA INITIO (675 mg) + a single 30 mg oral dose of aripiprazole, and provides an alternative to the concomitant three weeks of oral aripiprazole for initiation onto ARISTADA.

ARISTADA® and ARISTADA INITIO® are registered trademarks of Alkermes Pharma Ireland Limited.

INVEGA SUSTENNA® is a registered trademark of Johnson & Johnson.

[1] National Institutes of Health. 2010. *Schizophrenia Fact Sheet*. https://report.nih.gov/NIHfactsheets/Pdfs/Schizophrenia(NIMH).pdf. Accessed April 8, 2019.

[2] Saba DK, Levit KR, Elixhauser A. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs Hospital Stays Related to Mental Health, 2006 Statistical Brief #62 2006, Page 12, Figure 1

[3] Schizophrenia and Related Disorders Alliance of America, https://sardaa.org/resources/about-schizophrenia/ accessed on April 8, 2019.

[4] Olfson, M., Marcus, SC. and Doshi, JA. Continuity of Care After Inpatient Discharge of Patients with Schizophrenia in the Medicaid Program: A Retrospective Longitudinal Cohort Analysis. J Clin Psychiatry. 2010 Jul;71(7):831-8. doi: 10.4088/JCP.10m05969yel

[5] Heslin KC, Weiss AJ. Hospital Readmissions Involving Psychiatric Disorders, 2012. HCUP Statistical Brief #189. May 2015. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb189-Hospital-Readmissions-Psychiatric-Disorders-2012.pdf

[6] Lehman, A., Lieberman, J., et al. Practice Guideline for the Treatment of Patients with Schizophrenia; Second Edition. American Psychiatric Association, 2010

[7] Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. The nature of relapse in schizophrenia. BMC psychiatry, 2013;13(1), 50

[8] IQVIA NSP & Custom SOB data sets R12M ending September 2018

Alkermes Contacts:

For Investors:	Sandy Coombs,	+1 781 609 6377
For Media:	Marisa Borgasano,	+1 781 609 6659

View original content to download multimedia:http://www.prnewswire.com/news-releases/alkermes-announces-positive-topline-results-from-innovative-study-of-aristada-and-invega-sustenna-for-the-treatment-of-schizophrenia-300827587.html

SOURCE Alkermes plc