Alkermes Announces Positive Topline Results From ENLIGHTEN-Early Phase 3b Study of LYBALVI® in Patients Early in Illness

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- LYBALVI Demonstrated Less Weight Gain Compared to Olanzapine in Patients With Schizophrenia, Schizophreniform Disorder or Bipolar I Disorder -

DUBLIN, Feb. 8, 2022 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced positive topline results from ENLIGHTEN-Early, a phase 3b study that evaluated the effect of LYBALVI® (olanzapine and samidorphan) compared to olanzapine on body weight in young adult patients (ages 16 to 39; mean age: 26 years) with schizophrenia, schizophreniform disorder or bipolar I disorder who were early in their illness. The study met its pre-specified primary endpoint, as patients treated with LYBALVI experienced statistically significantly less weight gain than patients treated with olanzapine at Week 12 (mean percent change from baseline body weight: 6.77% for olanzapine vs. 4.91% for LYBALVI, p=0.012). Consistent with the ENLIGHTEN-2 pivotal study,[1] a numerical difference in average weight gain between treatment arms was observed early in treatment and continued to separate through the study's prespecified primary endpoint. LYBALVI is approved for the treatment of adults with schizophrenia, and for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes as monotherapy or an adjunct to lithium or valproate.

"We're pleased to share topline results from the ENLIGHTEN-Early study, in which LYBALVI demonstrated less mean weight gain compared to olanzapine in patients early in illness with schizophrenia, schizophreniform disorder or bipolar I disorder. These results complement the weight gain profile of LYBALVI shown in the ENLIGHTEN-2 pivotal study and reinforce the potential of LYBALVI as a new treatment option for adults living with schizophrenia or bipolar I disorder," said Craig Hopkinson, M.D., Executive Vice President of Research & Development and Chief Medical Officer at Alkermes.

"Olanzapine is well-known as an efficacious medicine but is often not used as a first-line treatment for early-in-illness patients due, in part, to concerns about weight gain," said Christoph Correll, M.D., Professor of Psychiatry and Molecular Medicine at Hofstra Northwell School of Medicine. "We're encouraged to see the positive results of this study in patients who have had less exposure to antipsychotic therapy and may be particularly susceptible to olanzapine-induced weight gain.[2]"

The study employed a hierarchical testing methodology for four pre-specified secondary endpoints. The first secondary endpoint did not achieve the pre-specified significance level, which precluded the assessment of statistical significance of the subsequent endpoints in the hierarchy. A numerical difference was observed between treatment arms across all secondary endpoints in favor of LYBALVI. Results of the secondary endpoints were as follows:

- The proportion of patients who gained 10% or more of their baseline body weight at three months was 30.4% for olanzapine vs. 21.9% for LYBALVI (p=0.075).
- The proportion of patients who gained 7% or more of their baseline body weight at three months was 44.8% for olanzapine vs. 33.1% for LYBALVI.
- The mean change from baseline in waist circumference at three months was 3.90 cm for patients treated with olanzapine vs. 2.99 cm for patients treated with LYBALVI.
- Treatment with LYBALVI was associated with improvements in symptoms of schizophrenia and bipolar I disorder over three months, as measured by the Clinical Global Impression of Severity (CGI-S) scale (mean change from baseline in CGI-S score of -0.82).

The safety profile of LYBALVI was consistent with previous studies. Overall, 63.5% of patients receiving LYBALVI and 63.3% of patients receiving olanzapine reported adverse events while on treatment. The most common adverse events reported for the LYBALVI treatment group were weight gain, somnolence and increased alanine aminotransferase and for the olanzapine treatment group were weight gain, somnolence and increased waist circumference. Serious adverse events occurred in 3.8% of LYBALVI patients and 3.7% of olanzapine patients during the treatment period. A majority of patients in both treatment groups completed the three-month study (78.2% of patients who received LYBALVI and 74.9% of patients who received olanzapine).

Alkermes expects to submit results from the ENLIGHTEN-Early study to a peer-reviewed journal for publication and present additional study results at upcoming scientific meetings.

ENLIGHTEN-Early Study Design

ENLIGHTEN-Early was a multicenter, randomized, double-blind, phase 3 study that evaluated the effect of LYBALVI compared to olanzapine on body weight over three months in young adults with schizophrenia, schizophreniform disorder or bipolar I disorder who were early in their illness. To qualify for participation as a patient "early in illness", subjects had to have less than 24 weeks of previous treatment with antipsychotics and less than four years elapse since the initial onset of active symptoms. A total of 428 patients (aged ≥16 and <40 years; mean: 26 years) were randomized in a 1:1 manner to receive either LYBALVI or olanzapine for up to 12 weeks, and the 408 patients who were dosed and had at least one post-baseline weight assessment were included in the full study population. The primary endpoint was percent change from baseline in body weight at Week 12. The hierarchical secondary endpoints at Week 12 consisted of: the proportion of patients with 10% or more weight gain from baseline, the proportion of patients with 7% or more weight gain from baseline, mean change from baseline in waist circumference and mean change from baseline in CGI-S

score within the LYBALVI treatment group.

All participants who completed the double-blind portion of the study were eligible to continue in an open-label, long-term safety extension study and receive LYBALVI for up to an additional 48 months of treatment. The objective of the extension study is to assess the long-term safety, tolerability and durability of effect of LYBALVI.

About Schizophrenia and Schizophreniform Disorder

Schizophrenia is a serious brain disorder marked by positive symptoms (hallucinations and delusions, disorganized speech and thoughts, and agitated or repeated movements) and negative symptoms (depression, blunted emotions and social withdrawal).[3] Schizophrenia affects approximately 1.1% of the U.S. population.[4] Schizophreniform disorder exhibits symptoms similar to schizophrenia but of shorter duration (one to six months).[3]

About Bipolar I Disorder

Bipolar disorder is a brain disorder that is marked by extreme changes in a person's mood, energy and ability to function. Individuals with this brain disorder may experience debilitating changes in mood from extreme highs (mania) to extreme lows (depression). Bipolar I disorder is characterized by the occurrence of at least one manic episode, with or without the occurrence of a major depressive episode, and affects approximately 1% of the adult population in the United States in any given year.[5]

About LYBALVI® (olanzapine and samidorphan)

LYBALVI® (olanzapine and samidorphan) is a once-daily, oral atypical antipsychotic drug approved in the U.S. for the treatment of adults with schizophrenia and for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or an adjunct to lithium or valproate. LYBALVI is composed of olanzapine, an established antipsychotic agent, co-formulated with samidorphan, a new chemical entity, in a single bilayer tablet. LYBALVI is available in fixed dosage strengths composed of 10 mg of samidorphan and 5 mg, 10 mg, 15 mg or 20 mg of olanzapine.

INDICATIONS and IMPORTANT SAFETY INFORMATION FOR LYBALVI® (olanzapine and samidorphan)

INDICATIONS

LYBALVI is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

IMPORTANT SAFETY INFORMATION

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

Contraindications: LYBALVI is contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal. If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis, including stroke, transient ischemia attack, and fatalities. See Boxed Warning above.

Precipitation of Severe Opioid Withdrawal in Patients who are Physiologically Dependent on Opioids: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids. Explain the risks associated with precipitated withdrawal and the importance of giving an accurate account of last opioid use to patients and caregivers.

Vulnerability to Life-Threatening Opioid Overdose: Attempting to overcome opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with LYBALVI or while transitioning off LYBALVI. In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia, discontinue LYBALVI. Opioids should be administered by properly trained individual(s) and patient should be continuously monitored in a setting equipped and staffed for cardiopulmonary resuscitation. Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome, a potentially fatal reaction. Signs and symptoms include hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation, intensive symptomatic treatment, and close monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a potentially fatal condition reported with exposure to olanzapine, a component of LYBALVI. Symptoms include a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue if DRESS is suspected.

Metabolic Changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Any patient treated with LYBALVI should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. In some cases,

hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required anti-diabetic treatment despite discontinuation of the suspect drug. Measure weight and assess fasting glucose and lipids when initiating LYBALVI and monitor periodically.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary, dyskinetic movements) and the likelihood it will become irreversible increases with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses, or after discontinuation. Given these considerations, LYBALVI should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. If signs and symptoms of TD appear, drug discontinuation should be considered.

Orthostatic Hypotension and Syncope: Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.

Falls: LYBALVI may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls, and consequently, fractures or other injuries. Assess patients for risk when using LYBALVI.

Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases): Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count or history of leukopenia or neutropenia. Discontinue LYBALVI if clinically significant decline in WBC occurs in the absence of other causative factors.

Dysphagia: Use LYBALVI with caution in patients at risk for aspiration.

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

Potential for Cognitive and Motor Impairment: Because LYBALVI may cause somnolence, impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including motor vehicles, until they are certain that LYBALVI does not affect them adversely.

Body Temperature Dysregulation: Use LYBALVI with caution in patients who may experience conditions that increase core body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, was associated with constipation, dry mouth, and tachycardia. Use LYBALVI with caution with other anticholinergic medications and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. In postmarketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: LYBALVI elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for a description of the risks for these products.

Most common adverse reactions observed in clinical trials were:

- *Schizophrenia (LYBALVI):* weight increased, somnolence, dry mouth, and headache
- *Bipolar I Disorder, Manic or Mixed Episodes (olanzapine):* asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine):* dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

Concomitant Medication: LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Concomitant use of LYBALVI is not recommended with strong CYP3A4 inducers, levodopa and dopamine agonists. Reduce dosage of LYBALVI when using with strong CYP1A2 inhibitors. Increase dosage of LYBALVI with CYP1A2 inducers. Use caution with diazepam, alcohol, other CNS acting drugs, or in patients receiving anticholinergic (antimuscarinic) medications. Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with LYBALVI. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LYBALVI during pregnancy.

Renal Impairment: LYBALVI is not recommended for patients with end-stage renal disease (eGFR of <15 mL/minute/1.73 m^2).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information, including Boxed Warning, for LYBALVI.

About Alkermes plc

Alkermes plc is a fully-integrated, global biopharmaceutical company developing innovative medicines in the fields of neuroscience and oncology. The company has a portfolio of proprietary commercial products focused on addiction, schizophrenia and bipolar I disorder, and a pipeline of product candidates in development for neurodegenerative disorders and cancer. 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 LYBALVI; and plans and expectations regarding presentation, and submission for publication of, results of the ENLIGHTEN-Early study. 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 clinical results for LYBALVI will be predictive of future clinical results or real-world results; whether LYBALVI could be shown to be 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, 2020 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.

References

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