# Alkermes Announces Topline Results From Long-Term, Open-Label Safety and Durability of Treatment Effect Study of LYBALVI® (olanzapine and samidorphan)

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*— Results Demonstrated that LYBALVI was Generally Well Tolerated With Stability of Body Weight and Metabolic Profile, and Durable Symptom Control, for Up to Four Years of Treatment —*

DUBLIN, Jan. 3, 2024 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced topline results from a phase 3, open-label extension study assessing the long-term safety, tolerability and durability of treatment effect of LYBALVI® (olanzapine and samidorphan) in patients with schizophrenia, schizophreniform disorder or bipolar I disorder for up to four years of treatment, following treatment received in prior LYBALVI studies. LYBALVI is 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 as adjunct to lithium or valproate.

In this global, open-label extension study, 523 participants received at least one dose of LYBALVI and 35.9% of participants completed the four-year treatment period. The safety profile of LYBALVI was consistent with previous studies. Patients' symptoms of schizophrenia or bipolar I disorder remained stable with up to four years of treatment with LYBALVI, as measured by the Clinical Global Impression of Severity (CGI-S) scale (mean change from baseline in CGI-S score of -0.28). Long-term treatment with LYBALVI was associated with minimal changes in body weight (mean change from baseline of +1.47 kg) and waist circumference (observed mean change from baseline of +0.61 cm) with up to four years of treatment. Similarly, there were generally minimal changes in lipid and glycemic parameters, including HDL cholesterol, LDL cholesterol, triglycerides, fasting glucose and HbA1c over the measured time period. Overall, 60% of patients reported an adverse event (AE). The most common AEs reported (>5%) were weight gain, headache, anxiety, insomnia, somnolence, nausea and weight decrease; most AEs were mild to moderate in severity.

"As clinicians, we see firsthand the challenges that people living with complex mental health conditions may face in finding treatment options that work for them long term, in terms of both efficacy and tolerability," said Jacob S. Ballon, M.D., M.P.H., Clinical Professor of Psychiatry and Behavioral Sciences at Stanford University and a study investigator. "These data, which demonstrated long-term tolerability and symptom control, as well as stability across key weight and metabolic factors, underscore LYBALVI's established safety and efficacy profile and provide important information for clinicians as we navigate treatment decisions with our patients in the real world."

"We are pleased to share the topline results from this long-term, open-label study. These data highlight the potential utility of LYBALVI as a foundational maintenance treatment option for people living with schizophrenia or bipolar I disorder and reinforce the safety profile of LYBALVI established in previous studies," said Craig Hopkinson, M.D., Executive Vice President, Research & Development and Chief Medical Officer at Alkermes. "In this study, patients taking LYBALVI experienced sustained treatment effect and tolerability, including stability across multiple metabolic parameters. Against the backdrop of average treatment persistency of less than six months for oral atypical antipsychotics generally, we are encouraged that more than one-third of subjects completed four years of treatment with LYBALVI."

Alkermes expects to submit results from this open-label, long-term study to a peer-reviewed journal for publication and to present additional study results at upcoming scientific meetings.

**Phase 3, Open-Label Study Design**

This was a multicenter, phase 3, open-label extension study assessing the long-term safety, tolerability and durability of treatment effect of LYBALVI for up to four years. Patients were eligible to enroll within seven days of completing one of three antecedent phase 3 clinical trials investigating LYBALVI: the ENLIGHTEN-1 safety extension study; the ENLIGHTEN-2 safety extension study (rollover extensions of the ENLIGHTEN-1 and ENLIGHTEN-2 phase 3 pivotal randomized controlled trials in adults with schizophrenia); and the 12-week ENLIGHTEN-Early randomized controlled trial comparing LYBALVI to olanzapine in young adults with recent-onset schizophrenia, schizophreniform disorder, or bipolar I disorder. In this long-term extension study, patients continued their daily dose of LYBALVI (olanzapine 5-20 mg + samidorphan 10 mg) from their antecedent study for up to an additional four years, with dose adjustments determined by the investigator. A total of 524 patients enrolled in the study, and 523 received ≥1 dose of LYBALVI. Baseline was established based on these 523 patients and changes as compared to baseline were based on those patients who completed four years of open-label treatment with LYBALVI. Patients were mostly male (61.6%) and White (72.7%), with a mean age of 35.1 years. Safety assessments included changes from baseline in body weight and waist circumference and the incidence of adverse events (AEs). Changes in lipid (high-density lipoprotein [HDL], low-density lipoprotein [LDL], and total cholesterol and triglycerides) and glycemic (glucose and glycosylated hemoglobin [$HbA_{1c}$]) parameters were evaluated. Antipsychotic efficacy was assessed using the Clinical Global Impressions–Severity (CGI-S) scale.

**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).[1] Schizophrenia affects approximately 1.1% of the U.S. population.[2] Schizophreniform disorder exhibits symptoms similar to schizophrenia, but without sufficient duration for a diagnosis of schizophrenia (one to six months).[1]

**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 mood states, including extreme highs (mania) and 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.[3]

**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 a combination of olanzapine, an atypical antipsychotic, and samidorphan, an opioid antagonist, 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.

**IMPORTANT SAFETY INFORMATION for LYBALVI® (olanzapine and samidorphan)**

**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 full Prescribing Information, including Boxed Warning, for LYBALVI.**

**About Alkermes plc**

Alkermes plc is a global biopharmaceutical company that seeks to develop innovative medicines in the field of neuroscience. The company has a portfolio of proprietary commercial products for the treatment of alcohol dependence, opioid dependence, schizophrenia and bipolar I disorder and a pipeline of clinical and preclinical candidates in development for neurological disorders. Headquartered in Dublin, Ireland, Alkermes has a research and development 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 for people living with schizophrenia or bipolar I disorder. 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 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, 2022 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.

LYBALVI ® is a registered trademark of Alkermes Pharma Ireland Limited, used by Alkermes, Inc. under license.

**References**

[1] American Psychiatric Association. Schizophrenia Spectrum and Other Psychiatric Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.

[2] Cloutier M. Journal of Clinical Psychiatry. 2016 Jun; 77(6): 764-71. https://www.psychiatrist.com/jcp/schizophrenia/economic-burden-schizophrenia-united-states-2013/

[3] Merikangas et al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, 2007 May; 64(5): 543-552. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1931566/

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