Findings From Long-Term Analysis of the Effects of LYBALVI® (olanzapine and samidorphan) on Negative Symptoms of Schizophrenia Published in The Journal of Clinical Psychiatry

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— 56-Week Post Hoc Analysis Demonstrated Sustained Reduction in Hard-to-Treat Negative Symptoms —

DUBLIN--(BUSINESS WIRE)--Apr. 14, 2026-- Alkermes plc (Nasdaq: ALKS) today announced the publication of a 56-week post hoc analysis of the effects of LYBALVI® (olanzapine and samidorphan) on negative symptoms in adults living with schizophrenia in the peer-reviewed publication *The Journal of Clinical Psychiatry*. The analysis—titled "The Efficacy of Olanzapine/Samidorphan on Negative Symptoms: A Post Hoc Analysis of 56-Week Treatment in Patients With Schizophrenia"—found that treatment with LYBALVI was associated with improvement in mean negative symptom scores. LYBALVI is approved in the U.S. for the treatment of schizophrenia in adults, and for the treatment of bipolar I disorder in adults, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or as adjunct to lithium or valproate. The full manuscript is now accessible online.

In schizophrenia, "positive symptoms" refer to an excess or distortion of normal function (such as delusions, hallucinations and disorganized thinking) while "negative symptoms" refer to a reduction or absence of normal behaviors (blunted affect, reduction in quantity of words spoken, reduced goal-directed activity due to decreased motivation, emotional or social withdrawal and diminished ability to experience pleasure). Negative symptoms are often associated with reduced functioning in patients with schizophrenia and can be a predictor of poor treatment response; addressing them remains a treatment challenge in schizophrenia.[1,2]

"Publication of this negative symptom post hoc analysis adds to a growing body of evidence supporting the role of LYBALVI in treating the complex symptomology related to schizophrenia," said Craig Hopkinson, M.D. (MBChB), Chief Medical Officer and Executive Vice President, Research & Development at Alkermes. "Alkermes remains committed to expanding the field's understanding of this challenging disease and the impact of medicine in helping patients manage their illness. We look forward to continued engagement with the scientific community in this important discourse."

Data from the post hoc analysis were derived from 281 adults who completed ENLIGHTEN-1—a 4-week inpatient study evaluating the efficacy, safety and tolerability of LYBALVI compared to olanzapine and placebo in patients experiencing an acute exacerbation of schizophrenia—and who subsequently enrolled in a 52-week open-label extension study (ENLIGHTEN-1 Extension) in which all patients received LYBALVI. Patient symptoms were assessed using the 30-item Positive and Negative Syndrome Scale (PANSS). This analysis looked at several subscales of the PANSS, including Negative Symptoms, Positive Symptoms and General Psychopathology Subscale scores and the Marder Negative Factor scores. LYBALVI demonstrated improvements from baseline in all subscale scores. In addition, the analysis looked at changes in two subgroups: in patients with prominent negative symptoms* (n=186) at baseline and in patients with predominant negative symptoms**/low positive symptoms (n=48) at baseline, in order to ascertain if the changes in negative symptoms were driven by changes in positive symptoms.

The analysis showed decreased negative symptoms over the first four weeks in a pooled analysis of treatment arms (LYBALVI, olanzapine and placebo) in ENLIGHTEN-1 with continued improvement over the 52 weeks of open-label treatment with LYBALVI.

- Baseline scores: The mean PANSS Negative Symptoms Subscale score at baseline was 25.7 and the mean Marder Negative Factor score at baseline was 25.2 in patients overall. The mean Marder Negative Factor score at baseline was 27.7 in the prominent negative symptoms subgroup and 28.2 in the predominant negative symptoms subgroup.
- Patients overall: Least squares (LS) mean changes from baseline in PANSS Negative Symptoms Subscale scores among all patients were −4.1 at week 4 and −7.6 at week 56. LS mean changes from baseline in Marder Negative Factor scores among all patients were −4.5 at week 4 and −8.2 at week 56.
- Prominent subgroup: Among patients with prominent negative symptoms at baseline, LS mean changes from baseline in PANSS Negative Symptoms Subscale scores were −4.6 at week 4 and −8.7 at week 56, and LS mean changes in Marder Negative Factor scores were −5.0 at week 4 and −9.6 at week 56.
- Predominant subgroup: A similar pattern of change was observed among patients with predominant negative symptoms at baseline. LS mean changes from baseline in Marder Negative Factor scores across patients in this subgroup were −4.7 at week 4 and −8.9 at week 56.

According to study author Christoph U. Correll, M.D., Professor of Psychiatry at The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, "LYBALVI has already been shown to provide the established efficacy of olanzapine as measured by PANSS total scores while mitigating olanzapine-associated weight gain and its effects on positive symptoms of schizophrenia have been evaluated. This post hoc analysis of the effect of LYBALVI on negative symptoms, which remain a persistent treatment challenge, further validates LYBALVI's utility for the treatment of schizophrenia, a condition characterized by complex symptom domains."

** Patients with prominent negative symptoms were defined as having a baseline Marder Negative Factor score ≥24.*

*** Patients with predominant negative symptoms/low positive symptoms were defined as having a baseline Marder Negative Factor score ≥24, PANSS scores ≥4 on two of the negative symptom items, and a PANSS Mohr Positive Factor score ≤19.*

About Schizophrenia

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]

About the Post Hoc Analysis of the ENLIGHTEN-1 and ENLIGHTEN-1 Extension Studies

This post hoc analysis examined data from patients who completed the ENLIGHTEN-1 study, a 4-week, placebo- and olanzapine-controlled study of LYBALVI for the treatment of acute schizophrenia, and who had at least one PANSS assessment in the 52-week, open-label ENLIGHTEN-1 Extension study in which all patients received LYBALVI. The analysis assessed the effects of up to 56 weeks of LYBALVI treatment on negative symptoms by integrating data across both studies. For the evaluation of the initial four weeks of treatment, data from the LYBALVI, placebo, and olanzapine treatment arms in ENLIGHTEN-1 were combined. Interpretation of the findings from this analysis is limited by the absence of a control group in ENLIGHTEN-1 Extension and by the fact that only patients meeting the ENLIGHTEN-1 enrollment criteria, specifically those initially experiencing an acute exacerbation of schizophrenia, were included. Additionally, the number of patients who met the criteria for predominant negative symptoms was relatively small.

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.

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.

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 creatine 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, and may 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.

Interference with Laboratory Tests for Opioid Detection: LYBALVI may cause false positive results with urinary immunoassay methods for detecting opioids. Use an alternative analytical technique (e.g., chromatographic methods) to confirm positive opioid urine drug screen results.

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):* somnolence, dry mouth, dizziness, asthenia, constipation, dyspepsia, increased appetite, and tremor
- *Bipolar I Disorder, Manic or Mixed Episodes, adjunct to lithium or valproate (olanzapine):* dry mouth, 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, a mid-cap growth and value equity, 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, bipolar I disorder and narcolepsy. Alkermes' pipeline includes late-stage clinical candidates in development for narcolepsy and idiopathic hypersomnia, and orexin 2 receptor agonists in early clinical development for other neurological disorders, including attention-deficit hyperactivity disorder (ADHD) and fatigue associated with multiple sclerosis and Parkinson's disease. Headquartered in Ireland, Alkermes also has a corporate office and research and development center in Massachusetts and a manufacturing facility in Ohio. For more information, please visit Alkermes' website at www.alkermes.com.

[1] Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*. 2020;16:519–534.

[2] Correll CU, Xiang P, Sarikonda K, et al. The economic impact of cognitive impairment and negative symptoms in schizophrenia: a targeted literature review with a focus on outcomes relevant to health care decision-makers in the United States. *J Clin Psychiatry*. 2024;85(3):24r15316.

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

[4] Cloutier M, Aigbogun MS, Guerin A, Nitulescu R, Ramanakumar AV, Kamat SA, DeLucia M, Duffy R, Legacy SN, Henderson C, Francois C, Wu E. The Economic Burden of Schizophrenia in the United States in 2013. *J Clin Psychiatry*. 2016 Jun;77(6):764-71.

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