Intra-Cellular Therapies Announces Publication of Lumateperone Pivotal Phase 3 Study in Bipolar Depression in The American Journal of Psychiatry

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In this study, lumateperone 42 mg showed significant reduction in depressive symptoms compared to placebo in patients with a major depressive episode associated with bipolar I or bipolar II disorder and a favorable safety and tolerability profile. These anti-depressant effects were statistically significant in both bipolar I and bipolar II disorder subgroup populations

Consistent with prior studies, weight changes were similar to placebo with no notable changes in metabolic or prolactin levels. Incidence of extrapyramidal symptoms related events were low and similar to placebo

These results, in conjunction with the positive results of Study 402 evaluating lumateperone 42 mg as adjunctive therapy with lithium or valproate, support lumateperone as a promising new treatment for patients with major depressive episodes associated with bipolar I or bipolar II disorder

The results of Studies 404 and 402 form the basis of CAPLYTA® (lumateperone) sNDAs for the treatment of bipolar depression currently under review with FDA; PDUFA target action date is December 17, 2021

NEW YORK, Sept. 27, 2021 (GLOBE NEWSWIRE) -- Intra-Cellular Therapies, Inc. (Nasdaq: ITCI), a biopharmaceutical company focused on the development and commercialization of therapeutics for central nervous system (CNS) disorders, today announced the publication of the results from its lumateperone monotherapy Phase 3 clinical trial (ITI-007-404). The article, "Efficacy and Safety of Lumateperone for Major Depressive Episodes Associated with Bipolar I or Bipolar II Disorder: A Phase 3 Randomized Placebo-Controlled Trial," was published online in The American Journal of Psychiatry and is available here.

"Bipolar depression represents the most prevalent and debilitating presentation of bipolar disorder. There is a critical need for more treatments that are effective and have favorable safety profiles," said Dr. Gary S. Sachs, Associate Clinical Professor in Psychiatry at Harvard Medical School and Founding Director of the Bipolar Clinic and Research Program at Massachusetts General. "The strong efficacy and impressive safety results reported in this trial for a broad patient population position lumateperone as a potentially important advancement in the treatment of this disorder."

"We are excited about the robust results seen across our bipolar depression program. The study reported on today, Study 404, our monotherapy study, along with Study 402, our adjunctive study with lithium or valproate form the basis of our supplemental NDAs under FDA review. If approved, we plan to to launch immediately and look forward to bringing CAPLYTA to market for the treatment of bipolar depression," said Dr. Sharon Mates, Chairman and CEO of Intra-Cellular Therapies.

Study 404 assesed the efficacy and safety of lumateperone as monotherapy in patients with bipolar I or bipolar II disorder experiencing a major depressive episode (bipolar depression). This global study randomized 381 patients with moderate to severe depression symptoms to receive placebo or lumateperone 42 mg for 6 weeks. The primary endpoint was the efficacy of 42 mg/day of lumateperone compared with placebo, measured by mean change from baseline to day 43 in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score.

In this clinical trial, treatment with lumateperone resulted in a substantial reduction in depressive symptoms. lumateperone 42mg was associated with a statically signficant greater reduction in MADRS score from baseline to day 43 (drug placebo difference -4.6 ($P<0.0001$; effect size = 0.56). Lumateperone 42 mg signficantly improved MADRS Total Score compared with placebo as early as week 1, the first time point measured, with continuing improvement throughout the study. Additionally, significant improvement in MADRS Total Score in the lumateperone group compared with placebo group at Day 43 was observed both in patients with bipolar I disorder and in those with bipolar II disorder.

Improvements were also seen in important secondary endpoints. Lumateperone 42 mg met the key secondary endpoint of statistically significant improvement on the CGI-BP-S Total Score ($p<0.0001$; effect size = 0.46) and on the CGI component that specifically assesses depression (CGI-BP-S Depression Score; $p<0.001$; effect size = 0.50).

Results support the favorable safety and tolerability profile of lumateperone. The most commonly reported adverse events occurring for lumateperone 42mg in >5% of patients and twice the rate in the placebo group were somnolence and nausea.

Lumateperone continues to report a favorable safety profile in important adverse events commonly asociated with antipsychotic therapy. Weight changes were similar to placebo with no notable changes in metabolic parameters including fasting glucose, cholesterol, triglycerides, insulin or prolactin levels. Incidence of extrapyramidal symptom related events were low and similar to placebo.

CAPLYTA® (lumateperone) is indicated for the treatment of schizophrenia in adults and has not been approved for other uses. CAPLYTA is available in 42 mg capsules.

Important Safety Information

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

Contraindications: CAPLYTA is contraindicated in patients with known hypersensitivity to lumateperone or any components of CAPLYTA. Reactions

have included pruritus, rash (e.g., allergic dermatitis, papular rash, and generalized rash), and urticaria.
Warnings & Precautions: Antipsychotic drugs have been reported to cause:

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis**, including stroke and transient ischemic attack. See Boxed Warning above.
- **Neuroleptic Malignant Syndrome (NMS)**, which is a potentially fatal reaction. Signs and symptoms include: high fever, stiff muscles, confusion, changes in breathing, heart rate, and blood pressure, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Patients who experience signs and symptoms of NMS should immediately contact their doctor or go to the emergency room.
- **Tardive Dyskinesia**, a syndrome of uncontrolled body movements in the face, tongue, or other body parts, which may increase with duration of treatment and total cumulative dose. TD may not go away, even if CAPLYTA is discontinued. It can also occur after CAPLYTA is discontinued.
- **Metabolic Changes**, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.
- **Leukopenia, Neutropenia, and Agranulocytosis (including fatal cases)**. Complete blood counts should be performed in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. CAPLYTA should be discontinued if clinically significant decline in WBC occurs in absence of other causative factors.
- **Decreased Blood Pressure & Dizziness**. Patients may feel lightheaded, dizzy or faint when they rise too quickly from a sitting or lying position (orthostatic hypotension). Heart rate and blood pressure should be monitored and patients should be warned with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.
- **Falls**. CAPLYTA may cause sleepiness or dizziness and can slow thinking and motor skills, which may lead to falls and, consequently, fractures and other injuries. Patients should be assessed for risk when using CAPLYTA.
- **Seizures**. CAPLYTA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold.
- **Sleepiness and Trouble Concentrating**. Patients should use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.
- **Body Temperature Dysregulation**. CAPLYTA should be used with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.
- **Dysphagia**. CAPLYTA should be used with caution in patients at risk for aspiration.

Drug Interactions: CAPLYTA should not be used with CYP3A4 inducers, moderate or strong CYP3A4 inhibitors and UGT inhibitors.

Special Populations: Newborn infants exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Breastfeeding is not recommended. Use of CAPLYTA should be avoided in patients with moderate or severe liver problems.

Adverse Reactions: The most common adverse reactions in clinical trials with CAPLYTA vs. placebo were somnolence/sedation (24% vs. 10%) and dry mouth (6% vs. 2%).
Please click here to see full Prescribing Information including **Boxed Warning**.

About CAPLYTA (lumateperone)

CAPLYTA 42mg/day is an oral, once daily atypical antipsychotic approved for the treatment of schizophrenia of adults. While the mechanism of action of CAPLYTA in the treatment of schizophrenia is unknown, the efficacy of CAPLYTA could be mediated through a combination of antagonist activity at central serotonin 5-HT2A receptors and postsynaptic antagonist activity at central dopamine D2 receptors.

Lumateperone is being investigated for the treatment of bipolar depression, major depressive disorder, and other neuropsychiatric and neurological disorders. Lumateperone is not FDA-approved for these disorders.

About Intra-Cellular Therapies

Intra-Cellular Therapies is a biopharmaceutical company founded on Nobel prize-winning research that allows us to understand how therapies affect the inner-workings of cells in the body. The company leverages this intracellular approach to develop innovative treatments for people living with complex psychiatric and neurologic diseases. For more information, please visit www.intracellulartherapies.com.

Forward-Looking Statements

This news release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, our plans to commercialize CAPLYTA for bipolar depression immediately following approval; whether clinical trial results will be predictive of future real-world results; our beliefs about the potential utility of our product candidates; and development efforts and plans under the caption “About Intra-Cellular Therapies.” All such forward-looking statements are based on management's present expectations and are subject to certain factors, risks and uncertainties that may cause actual results, outcome of events, timing and performance to differ materially from those expressed or implied by such statements. These risks

and uncertainties include, but are not limited to, the following: there are no guarantees that CAPLYTA will be commercially successful; we may encounter issues, delays or other challenges in commercializing CAPLYTA; the COVID-19 pandemic may negatively impact our commercial plans and sales for CAPLYTA; the COVID-19 pandemic may negatively impact the conduct of, and the timing of enrollment, completion and reporting with respect to, our clinical trials; whether CAPLYTA receives adequate reimbursement from third-party payors; the degree to which CAPLYTA receives acceptance from patients and physicians for its approved indication; challenges associated with execution of our sales activities, which in each case could limit the potential of our product; results achieved in CAPLYTA in the treatment of schizophrenia following commercial launch of the product may be different than observed in clinical trials, and may vary among patients; any other impacts on our business as a result of or related to the COVID-19 pandemic; risks associated with our current and planned clinical trials; we may encounter unexpected safety or tolerability issues with CAPLYTA following commercial launch for the treatment of schizophrenia or in ongoing or future trials and other development activities; our other product candidates may not be successful or may take longer and be more costly than anticipated; product candidates that appeared promising in earlier research and clinical trials may not demonstrate safety and/or efficacy in larger-scale or later clinical trials or in clinical trials for other indications; our proposals with respect to the regulatory path for our product candidates may not be acceptable to the FDA; our reliance on collaborative partners and other third parties for development of our product candidates; and the other risk factors detailed in our public filings with the Securities and Exchange Commission. All statements contained in this press release are made only as of the date of this press release, and we do not intend to update this information unless required by law.

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