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Results from a clinical phase III study of once-monthly aripiprazole IM depot formulation for the maintenance treatment of schizophrenia presented at APA

- *Data from phase III trial demonstrated improvement in time to relapse, the primary efficacy endpoint for patients receiving once-monthly aripiprazole IM depot formulation compared to placebo*
- *Results presented at 165th Annual Meeting of the American Psychiatric Association*
- *Long-term disease maintenance is the ultimate goal of treating the many adults living with schizophrenia globally*

H. Lundbeck A/S (Lundbeck) and Otsuka Pharmaceutical Co., Ltd. (Otsuka) today announced results from a clinical phase III clinical trial evaluating the efficacy, safety and tolerability of once-monthly aripiprazole intramuscular (IM) depot formulation for the maintenance treatment of adults with schizophrenia. Trial results were presented in four poster presentations at the 165th Annual Meeting of the American Psychiatric Association (APA) in Philadelphia, USA.

In a 52-week, double-blind, randomized, placebo-controlled study, aripiprazole IM depot significantly delayed time-to-impending relapse compared to placebo, the primary endpoint of the study (Hazard ratio = 5.03, $p < 0.0001$). In addition, improvements in the symptoms [as measured by the Positive and Negative Syndrome Scale (PANSS) total score] were maintained throughout the study in patients treated with aripiprazole IM depot formulation, while patients who received placebo reported significantly worsening scores (mean change from baseline at week 52 was 1.4 for aripiprazole IM depot compared to 11.6 for placebo; LOCF analysis, $p < 0.0001$). Results also demonstrated that aripiprazole IM depot was well tolerated, with a discontinuation rate due to treatment-related adverse events less than placebo (7.1% vs. 13.4%, respectively).

"Otsuka and Lundbeck are committed to advancing care and addressing unmet needs for patients with schizophrenia," said William H. Carson, M.D., President and CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. *"We are pleased to report on the positive data from the pivotal Phase 3 study designed to evaluate the efficacy and tolerability of aripiprazole IM depot as a long-term maintenance treatment for patients with schizophrenia."*

"We are very encouraged by these data of aripiprazole IM depot formulation which shows that a once-monthly injection of this compound is effective in delaying the time to relapse for patients with schizophrenia" says Executive Vice President Anders Gersel Pedersen, Head of Research & Development at Lundbeck, and continues: *"As relapsed patients experience further erosion of his or her*

mental and overall physical health, which again can lead to decreased functioning, increased morbidity and thereby worsen the overall outcome."

Study design and findings

This clinical phase III multi-center, double-blind, placebo-controlled study included 710 adult patients with schizophrenia who required chronic treatment with an antipsychotic agent. The study was designed to assess the efficacy, safety and tolerability of aripiprazole IM depot formulation, as a long-term maintenance treatment for schizophrenia. In addition, due to the placebo-controlled nature of the study, an interim analysis was conducted after 50% of the targeted events of impending relapse were accrued. An independent Data Monitoring Committee evaluated the data from this interim analysis and determined that the study should be stopped based on meeting pre-specified efficacy criteria. The data reported here represent the final data analysis following termination of the study.

The study was comprised of four phases: 1) an oral conversion phase (4-6 weeks) in which study patients not currently being treated with aripiprazole were converted to oral aripiprazole monotherapy; 2) an oral stabilization phase (4-12 weeks) in which all patients were treated with oral aripiprazole (10-30mg/day) until achieving pre-specified stability criteria for at least 4 weeks; 3) an IM depot stabilization phase where patients received aripiprazole IM depot injections every four weeks (400 mg with a permissible single decrease to 300 mg, with co-administration of oral aripiprazole during the first two weeks (n=576) ; and 4) a maintenance treatment phase where patients received an injection of aripiprazole IM depot or placebo once every 4 weeks for 52 weeks (n=403). When patients participating in Phase 3 of the study met stability criteria for 12 weeks they were randomized (2:1) to aripiprazole IM depot (n=269) or placebo (n=134) for the maintenance phase (Phase 4).

The primary efficacy endpoint was time to impending relapse. The key secondary efficacy endpoint was the percentage of subjects who met the impending relapse criteria at the endpoint of the Double-blind, Placebo-controlled Phase. Other secondary efficacy evaluations included mean changes from baseline in PANSS, as well as mean changes from baseline in the Personal and Social Performance (PSP) scale scores, Clinical Global Impression of Severity (CGI-S) scores and in the Investigator's Assessment Questionnaire (IAQ) scores, a scale designed to evaluate response to antipsychotics. Tolerability and safety also were assessed.

In addition to delayed time-to-impending relapse, the rate of impending relapse was significantly lower with aripiprazole IM depot compared to placebo after 52 weeks of treatment (10.0% vs. 39.6%, respectively; $p < 0.0001$). Improvements in symptoms, functioning and overall response to treatment that were achieved during the stabilization phase were sustained during the maintenance treatment phase of the study:

- During the maintenance treatment phase, PANSS subscale scores showed both positive and negative symptom stability with aripiprazole IM depot but showed significant worsening for patients who received placebo [mean change from baseline in PANSS positive symptom subscale scores was 0.4 for aripiprazole IM depot compared to a mean change of 4.3 for placebo (LOCF analysis, $p < 0.0001$); and a mean change in baseline of 0.2 vs. 1.6 for PANSS negative subscale scores (LOCF analysis, $p < 0.0001$)].

- Mean change from baseline in PSP scale scores during the maintenance treatment phase of the study showed greater stability of social functioning with aripiprazole IM depot compared to placebo (-1.7 vs. -6.2, respectively; LOCF analysis, $p=0.0002$).
- Mean change from baseline in the IAQ (a 12-item assessment of overall effectiveness) total scores also remained more stable amongst patients who received aripiprazole IM depot than those receiving placebo during the maintenance treatment phase (mean change was +1.3 for aripiprazole IM depot vs. +3.8 for placebo; LOCF analysis, $p<0.0001$).

Similar adverse events (AEs) were reported across all phases of the study for aripiprazole or aripiprazole IM depot and placebo. Most AEs were mild to moderate and severe AEs were rare (<5.0% incidence for aripiprazole or aripiprazole IM depot in all phases; the incidence of severe AEs in the maintenance phase was 4.1% for aripiprazole IM depot vs. 6.7% for placebo). The most common treatment-emergent AEs (occurring in > 5% of aripiprazole IM depot patients and greater than placebo) during the maintenance treatment phase were: insomnia (10.0% vs. 9.0%); tremor (5.9% vs. 1.5%); and headache (5.9% vs. 5.2%). The incidence of injection site pain was 3.0% for aripiprazole IM depot and 3.7% for placebo in the maintenance treatment phase. The incidence of clinically relevant weight gain (> 7% increase from baseline) was 6.4% for aripiprazole IM depot vs. 5.2% for placebo (LOCF analysis).

About aripiprazole IM depot formulation

Aripiprazole IM depot is a sterile lyophilized cake that, when reconstituted with sterile water for injection, forms an injectable suspension. On 22 November, 2011, Otsuka announced that the US Food and Drug Administration (FDA) determined that the company's new drug application (NDA) for investigational once-monthly aripiprazole IM depot formulation for the indication of maintenance treatment of schizophrenia in adults was sufficiently complete to permit a substantive review. Otsuka and Lundbeck have entered into a long-term agreement in the field of central nervous system disorders and the two companies will collaborate on the development and commercialization (following approval of regulatory authorities) of aripiprazole IM depot formulation worldwide.

Financial guidance

The content of this release will have no influence on the Lundbeck Group's financial guidance for 2012 which was provided on 8 February 2012 in connection with the release of the financial results for 2011.

IMPORTANT SAFETY INFORMATION for ABILIFY® (aripiprazole)

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. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Suicidality and Antidepressant Drugs

Children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders are at increased risk of suicidal thinking and behavior. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS

Contraindication – Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis.

- Cerebrovascular Adverse Events, Including Stroke: Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack, including fatalities)
- Neuroleptic Malignant Syndrome (NMS): As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status
- Tardive Dyskinesia (TD): The risk of developing TD 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
- 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 including ABILIFY
 - 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. When treating pediatric patients, weight gain should be monitored and assessed against expected normal growth

Orthostatic Hypotension – Use with caution in patients with known cardiovascular or cerebrovascular disease or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotics, including ABILIFY.

Seizures/Convulsions: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (eg, Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

Body Temperature Regulation – Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

Suicide – The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients.

Dysphagia – Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.
Physicians should advise patients to avoid alcohol while taking ABILIFY.

Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder. If a strong CYP3A4 inhibitor and strong CYP2D6 inhibitor are coadministered or a known CYP2D6 poor metabolizer is receiving a concomitant strong CYP3A4 inhibitor, the ABILIFY dose should be reduced to one-quarter (25%) of the usual dose.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

Commonly observed adverse reactions: ($\geq 5\%$ incidence and at least twice the rate of placebo for ABILIFY vs placebo, respectively):

- Adult patients with Major Depressive Disorder (adjunctive treatment to antidepressant therapy): akathisia (25% vs 4%), restlessness (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)
- Adult patients (monotherapy) with Bipolar Mania: akathisia (13% vs 4%), sedation (8% vs 3%), tremor (6% vs 3%), restlessness (6% vs 3%), and extrapyramidal disorder (5% vs 2%)
- Adult patients (adjunctive therapy with lithium or valproate) with Bipolar Mania: akathisia (19% vs 5%), insomnia (8% vs 4%), and extrapyramidal disorder (5% vs 1%)
- Pediatric patients (10 to 17 years) with Bipolar Mania: somnolence (23% vs 3%), extrapyramidal disorder (20% vs 3%), fatigue (11% vs 4%), nausea (11% vs 4%), akathisia (10% vs 2%), blurred vision (8% vs 0%), salivary hypersecretion (6% vs 0%), and dizziness (5% vs 1%)
- Adult patients with Schizophrenia: akathisia (8% vs 4%)
- Pediatric patients (13 to 17 years) with Schizophrenia: extrapyramidal disorder (17% vs 5%), somnolence (16% vs 6%), and tremor (7% vs 2%)
- Pediatric patients (6 to 17 years) with irritability associated with Autistic Disorder: sedation (21% vs 4%), fatigue (17% vs 2%), vomiting (14% vs 7%), somnolence (10% vs 4%), tremor (10% vs 0%), pyrexia (9% vs 1%), drooling (9% vs 0%), decreased appetite (7% vs 2%), salivary hypersecretion (6% vs 1%), extrapyramidal disorder (6% vs 0%), and lethargy (5% vs 0%)
- Adult patients with agitation associated with Schizophrenia or Bipolar Mania: nausea (9% vs 3%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Non-Teratogenic Effects – Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. ABILIFY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNINGS, for ABILIFY or visit www.ABILIFY.com.



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About Otsuka Pharmaceutical Co. Ltd.

Founded in 1964, Otsuka Pharmaceutical Co., Ltd. is a global healthcare company with the corporate philosophy: 'Otsuka-people creating new products for better health worldwide.' Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and consumer products for the maintenance of everyday health. Otsuka is committed to being a corporation that creates global value, adhering to the high ethical standards required of a company involved in human health and life, maintaining a dynamic corporate culture, and working in harmony with local communities and the natural environment.

Otsuka Pharmaceutical Co., Ltd. is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group. The Otsuka Group has business operations in 23 countries and regions around the world, with consolidated sales of JPY 1,090.2 billion for fiscal year 2010.

About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUKY) is an international pharmaceutical company highly committed to improving the quality of life for people suffering from brain disorders. For this purpose, Lundbeck is engaged in the research, development, production, marketing and sale of pharmaceuticals across the world. The company's products are targeted at disorders such as depression and anxiety, psychotic disorders, epilepsy and Huntington's, Alzheimer's and Parkinson's diseases.

Lundbeck was founded in 1915 by Hans Lundbeck in Copenhagen, Denmark. Today Lundbeck employs approximately 6,000 people worldwide. Lundbeck is one of the world's leading pharmaceutical companies working with brain disorders. In 2011, the company's revenue was DKK 16.0 billion (approximately EUR 2.1 billion or USD 3.0 billion). For more information, please visit www.lundbeck.com.