

## For Immediate Release

Company name Otsuka Holdings Co., Ltd.  
Representative Tatsuo Higuchi  
President and Representative Director, CEO  
Code number 4578 First Section, Tokyo Stock Exchange  
Inquiries Takuma Kimura  
Director, Investors Relations Department

### **RESULTS FROM A PHASE 3 STUDY OF ONCE-MONTHLY ARIPIPRAZOLE INTRAMUSCULAR (IM) DEPOT FORMULATION FOR THE MAINTENANCE TREATMENT OF SCHIZOPHRENIA PRESENTED AT APA ANNUAL MEETING**

- Data from Phase 3 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

**Tokyo, Japan, May 8, 2012** -- Otsuka Pharmaceutical Co., Ltd. (Head Office: Chiyoda-ku, Tokyo, Japan; President: Taro Iwamoto), a wholly owned direct subsidiary of Otsuka Holdings Co., Ltd., today announced results from a Phase 3 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 2012 American Psychiatric Association (APA) Annual Meeting in Philadelphia.

The primary efficacy results are in press and will be published in the May 2012 issue of the *Journal of Clinical Psychiatry* (available online at <http://dx.doi.org/10.4088/JCP.11m07530>).

In a 52-week, double-blind, randomized, placebo-controlled study conducted by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC), aripiprazole IM depot formulation 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 formulation compared to 11.6 for placebo; LOCF analysis,  $p < 0.0001$ ).

“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, OPDC. “We are pleased to report positive data from the pivotal Phase 3 study designed to evaluate the efficacy, safety and tolerability of aripiprazole IM depot formulation as a long-term maintenance treatment for patients with schizophrenia.”

“Long-term disease management is the ultimate goal of treating the nearly 2.2 million adults living with schizophrenia in the U.S.,” said study investigator John M. Kane, M.D., Chairman of Psychiatry, The Zucker Hillside Hospital, and Vice President, Behavioral Health Services, North Shore-LIJ Health System. “Every relapse a patient experiences can cause further erosion of his or her mental and physical health. These

study results demonstrate that a once-monthly injection of aripiprazole IM depot formulation is effective in delaying the time to relapse for patients with schizophrenia.”

Commenting on the first data coming from the long-term alliance established between Otsuka and Lundbeck, Anders Gersel Pedersen, Executive Vice President and Head of Research & Development at Lundbeck added, “As two companies with deep expertise in central nervous system disorders, Otsuka and Lundbeck are tackling some of the most complex mental health conditions, including schizophrenia. The presentation of these data is the first of many steps we envision taking as a collaboration committed to advancing mental health drug development over the coming decade.”

### **Study Design and Findings**

This Phase 3 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 formulation stabilization phase where patients received aripiprazole IM depot formulation 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 formulation 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 formulation (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 formulation 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 formulation 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 formulation 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 formulation 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 formulation than those receiving placebo during the maintenance treatment phase (mean change was +1.3 for aripiprazole IM depot formulation 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 formulation and placebo. Most AEs were mild to moderate and severe AEs were rare (<5.0% incidence for aripiprazole or aripiprazole IM depot formulation in all phases; the incidence of severe AEs in the maintenance phase was 4.1% for aripiprazole IM depot formulation vs. 6.7% for placebo). The most common treatment-emergent AEs (occurring in  $\geq 5\%$  of aripiprazole IM depot formulation 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 formulation 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 formulation vs. 5.2% for placebo (LOCF analysis). Discontinuation rates due to treatment-related adverse events were 7.1% for aripiprazole IM depot formulation vs. 13.4% for placebo.

### **About Aripiprazole IM Depot Formulation**

Aripiprazole IM depot formulation is a sterile lyophilized cake that, when reconstituted with sterile water for injection, forms an injectable suspension. On November 22, 2011, Otsuka announced that the U.S. Food and Drug Administration (FDA) determined that the company's new drug application (NDA) for investigational once-monthly aripiprazole depot formulation for the indication of maintenance treatment of schizophrenia in adults was sufficiently complete to permit a substantive review. Otsuka Pharmaceutical Co., Ltd. and H. Lundbeck A/S 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 depot formulation worldwide.

While the use of aripiprazole IM depot formulation is investigational, aripiprazole is currently approved and marketed as ABILIFY® (aripiprazole). ABILIFY is indicated for:

- Use as an adjunctive therapy to antidepressants in adults with Major Depressive Disorder who have had an inadequate response to antidepressant therapy
- Acute treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy and as an adjunct to lithium or valproate in adult and pediatric patients 10 to 17 years of age
- Maintenance treatment of Bipolar I Disorder, both as monotherapy and as an adjunct to lithium or valproate
- Treatment of Schizophrenia in adults and adolescents 13 to 17 years of age
- Treatment of irritability associated with Autistic Disorder in pediatric patients 6 to 17 years of age

### Special Considerations for Pediatric Uses:

- Treatment for pediatric patients should be initiated only after a thorough diagnostic evaluation and careful consideration of the risks and benefits of treatment. Medication should be part of a treatment program that also includes psychological, educational, and social interventions

ABILIFY Injection is indicated for:

- Acute treatment of agitation associated with Schizophrenia or Bipolar Disorder, manic or mixed in adults

## **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](http://www.ABILIFY.com).

#### **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 ¥1,090.2 billion for fiscal year 2010.

#### **About Otsuka Pharmaceutical Development & Commercialization, Inc.**

Otsuka Pharmaceutical Development & Commercialization, Inc. is involved in conducting all phases of clinical research and development of innovative healthcare products to address unmet medical needs. OPDC is well established in the scientific community as a globally focused organization that plays a leadership role in the research and development of Otsuka's ethical healthcare products.

The Company is dedicated to the improvement of the quality of human life and health of patients around the world with a strong commitment to research and development in the areas of cardiovascular, gastrointestinal, respiratory, renal and neuroscience systems, and to treat cancer and ophthalmic disorders. OPDC is part of the Otsuka Group companies. For more information, visit [www.otsuka-us.com](http://www.otsuka-us.com).

OPDC is a subsidiary of Otsuka America, Inc. (OAI), which is wholly owned by Otsuka Pharmaceutical Co., Ltd. (OPC).

#### **About H. Lundbeck A/S**

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's U.S. business is based in Deerfield, Illinois. To learn more about Lundbeck in the U.S., visit [www.lundbeckus.com](http://www.lundbeckus.com).

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 2.2 billion or USD 3.0 billion). For more information, please visit [www.lundbeck.com](http://www.lundbeck.com).