

# Data Demonstrate Aripiprazole Significantly Improved Symptoms Of Acute Mania in Patients With Bipolar Disorder; New Data Presented Today at American Psychiatric Association Annual Meeting

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## Body

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Patients with bipolar disorder who received treatment with aripiprazole, an investigational antipsychotic medication, showed significant improvement in symptoms of acute mania, according to a new study presented today at the 155th Annual Meeting of the American Psychiatric Association. The placebo-controlled study also showed that aripiprazole has a rapid onset of action, significantly reducing symptoms of acute mania by day four of treatment. Aripiprazole was well tolerated, with discontinuations of therapy due to adverse events similar to placebo. Additionally, there was no significant difference in the incidence of clinically meaningful weight change in patients treated with aripiprazole and placebo.

"In this study, aripiprazole demonstrated rapid onset of symptom improvement, which is very important when treating manic episodes," according to lead investigator Paul E. Keck, Jr., MD, Department of Psychiatry, University of Cincinnati College of Medicine. "We look forward to more data in the treatment of bipolar mania."

Aripiprazole was studied in a Phase III multicenter, double-blind, randomized, placebo-controlled study with 262 patients diagnosed with acute mania. Beginning at day four, aripiprazole was significantly better than placebo in reducing acute manic symptoms, such as elevated mood, irritability, thought disorder, abnormal thought content and disruptive-aggressive behavior ( $p=0.004$ ). This separation increased during the three-week treatment period as measured by mean change from baseline in the total score on the Young Mania Rating Scale (Y-MRS) (week three Y-MRS total score decreased by 8.15 and 3.35 for aripiprazole and placebo respectively,  $p=0.002$ ). Furthermore, 40 percent of patients treated with aripiprazole responded to treatment, compared to 19 percent of patients treated with placebo ( $p=0.001$ ). In this study, response was defined as a decrease of greater than or equal to 50 percent in Y-MRS total score. In a second placebo-controlled study, aripiprazole demonstrated symptom improvement comparable to that of the study previously described; however, due to a high placebo response rate (approximately 40 percent), aripiprazole did not show statistical separation from placebo. The most commonly observed adverse events associated with aripiprazole were headache, nausea, dyspepsia, somnolence and agitation, whereas the most common adverse events associated with placebo were headache, agitation, nausea, dyspepsia and anxiety. The majority of somnolence and these gastrointestinal events occurred during the

first week of treatment and very few events lasted more than 7 days. Adverse events reported in the two studies were similar.

"There are significant unmet needs in the treatment of serious mental illness," said Peter R. Dolan, Chairman and Chief Executive Officer, Bristol-Myers Squibb Company. "We are very encouraged by the clinical research being conducted with aripiprazole to help meet the needs of patients with psychiatric disorders."

Bristol-Myers Squibb and Otsuka Pharmaceuticals filed regulatory applications for aripiprazole for an indication for treatment of schizophrenia in the U.S. and Europe in October and December 2001, respectively. The companies are currently conducting clinical trials with aripiprazole in psychotic illnesses such as schizophrenia, bipolar disorder and psychosis associated with Alzheimer's disease.

Aripiprazole is believed to have a mechanism of action that is fundamentally different from available antipsychotics. Aripiprazole exhibits potent partial agonism of D2 dopamine receptors, and is also associated with partial agonism of 5HT(1A) serotonin receptors and antagonism of 5HT(2A) serotonin receptors. Partial agonism refers to the ability to both block a receptor if it is overstimulated and to stimulate a receptor when activity is needed.

"We are proud to have discovered this compound," said Tatsuo Higuchi, President, Otsuka Pharmaceutical Co., Ltd. "We look forward to working with Bristol-Myers Squibb to developing aripiprazole to its fullest potential."

#### Serious and Persistent Mental Illness

Bipolar disorder, also known as manic-depressive disorder, affects nearly 2 million Americans, and like schizophrenia, generally strikes before the age of 30.(1) A person with bipolar disorder experiences mood episodes, which can include manic episodes, depressive episodes and mixed episodes.

Manic episodes typically involve either extreme happiness or irritability accompanied by other changes in behavior, such as increased activity, decreased need for sleep, grandiose thinking and racing thoughts. During depressive episodes, individuals usually experience sadness, diminished interest in usual activities and disturbances in sleep, appetite, energy and concentration. Mixed episodes involve the simultaneous occurrence of depressive and manic symptoms. Sometimes individuals with bipolar disorder experience psychotic symptoms (such as delusions and hallucinations) during the mood episodes, but these psychotic symptoms go away as the episode resolves.

The duration of mood episodes range from hours to many months. Between episodes, people with bipolar disorder often return to their usual level of functioning and may have minimal to no residual symptoms. Some people with the disorder can enjoy healthy, stable mood for many years between episodes, while others rapidly go in and out of mood episodes almost continually, while still others experience mood episodes at frequencies between these two extremes.(2)

#### About Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.

Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd. are collaborative partners in the development and commercialization of aripiprazole in the United States and major European countries. Otsuka discovered aripiprazole.

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Bristol-Myers Squibb is a \$19 billion pharmaceutical and related health care products company whose mission is to extend and enhance human life.

Founded 38 years ago, Otsuka Pharmaceuticals is a diversified health care company guided by its philosophy: "Otsuka, people creating new products for better health worldwide" and dedicated to the research and development of innovative medical, pharmaceutical, and nutritional consumer products to improve the quality of human life. Otsuka Pharmaceuticals has a diverse portfolio including central nervous system, cardiovascular, circulatory, gastro-intestinal, respiratory, dermatological, ophthalmologic, anti-cancer therapies, and is pursuing research in genomics and protein function. Otsuka is comprised of 32 businesses and 19,000 employees around the world, earning total revenues of \$4.5 billion annually.

Upon regulatory approval, aripiprazole would be marketed worldwide by Otsuka Pharmaceuticals and Bristol-Myers Squibb. Aripiprazole was discovered by Otsuka Pharmaceutical Co., Ltd.

Visit Bristol-Myers Squibb on the World Wide Web at: <http://www.bms.com>

Visit Otsuka Pharmaceutical Co., Ltd. at: <http://www.otsuka.co.jp>

(1) Symptoms & Causes of Manic Depression (Bipolar Disorder), National Mental Health Association website (<http://www.healthtouch.com>)

(2) An Introduction to Bipolar Disorder, Johns Hopkins Medicine website (<http://www.hopkinsmedicine.org>)

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