



## Study Suggests Risperidone Long-Acting Injection Combined with Standard Treatment Helped Delay Time to Relapse in Patients with Bipolar Disorder

MONTREUX, Switzerland, Feb 04, 2008 /PRNewswire via COMTEX News Network/ -- Patients with frequently relapsing bipolar disorder had a significant delay in the time to an initial relapse when risperidone long-acting injection (RLAI) was combined with standard treatment, according to a new study. The study compared patients who received RLAI and standard treatment to those who received standard treatment combined with placebo.

The study was presented yesterday at the 14th Biennial Winter Workshop on Schizophrenia and Bipolar Disorders in Montreux, Switzerland.(1) This one-year, phase 3, trial is the first placebo-controlled study to explore the use of a long-acting injection medication in the maintenance treatment of frequently relapsing bipolar disorder (FRBD). FRBD, defined as four or more manic or depressive episodes in the previous year that require a doctor's care, may affect 20% of the 27 million people with bipolar disorder worldwide(2,3).

The study compared the time to the next mood episode, also known as a relapse, in FRBD patients receiving RLAI plus standard treatment vs. patients receiving placebo plus standard treatment. For most patients, standard treatment consisted of mood stabilizers, antidepressants, anxiolytics or combinations thereof. The trial showed that time to relapse was significantly longer in patients receiving RLAI compared with placebo ( $p=0.004$ ) and the relative risk of relapse was 2.4 times higher with placebo. The relapse rates were 47.8% with placebo and 22.2% with RLAI.

"Patients with frequently relapsing bipolar disorder require more healthcare interventions than patients with fewer episodes, and there is a huge unmet need for new treatments," said Dr. Joseph Calabrese, Co-Director of the Bipolar Disorders Research Center, University Hospitals Case Medical Center, Case Western Reserve University. Dr. Calabrese is a consultant to the study sponsors, Ortho-McNeil Janssen Scientific Affairs, L.L.C. "Risperidone long-acting injection is administered once every two weeks by a healthcare professional and avoids the need for patients to remember to take daily antipsychotic medications."

In the study, 139 patients were randomized to receive either RLAI 25-50mg intramuscular injection ( $n=72$ ), or placebo injections ( $n=67$ ) adjunctive to standard treatment. Patients receiving RLAI plus standard treatment were eligible to enter the double blind phase of the trial if they met predefined criteria(a) for being stable the last four weeks of the 16-week open-label stabilization phase.

In the study, Frequently Relapsing Bipolar Disorder: Evidence for an Effective Treatment Using Adjunctive Risperidone Long-Acting Injectable, 67% of patients randomized received a 25 mg dose of RLAI, 29% received a 37.5 mg dose and 4% received a 50 mg dose, administered once every two weeks.

The primary efficacy endpoint in the double-blind phase of the trial was the time from randomization to relapse, where relapse was defined as the first occurrence of a mood episode as determined by an independent Relapse Monitoring Board (RMB).(b)

The results showed a significant difference in time to relapse ( $p=0.004$ ), with a more than two-fold higher risk of relapse in the placebo group (47.8%) than the RLAI group (22.2%). In addition, scores on the Clinical Global Impression-Bipolar-Severity (CGI-BP-S) scale for overall bipolar disorder and the Clinical Global Impression-Bipolar-Change (CGI-BP-C) scale worsened significantly ( $p<0.05$ ) in the placebo group compared with the RLAI group.

Treatment-emergent adverse effects (TEAEs) occurred more frequently in the group that received placebo and standard treatment (76.1%) than in the group that received RLAI and standard treatment (70.8%), as did serious adverse effects (placebo=19.4%; RLAI = 13.9%). The most common TEAEs (greater than 5%) in the double-blind phase were tremor (RLAI = 23.6%; placebo = 16.4%), insomnia (RLAI = 19.4%; placebo = 23.9%), muscle rigidity (RLAI = 11.1%; placebo = 6%); weight gain (RLAI = 6.9%; placebo = 1.5%) and hypokinesia (RLAI = 6.9%; placebo = 0%). A total of 5 patients discontinued due to adverse events in the double-blind phase (3 in the RLAI group and 2 in the placebo group).

Risperidone long-acting injection is marketed in the U.S. by Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. The formulation is manufactured by Alkermes, Inc. (Nasdaq: ALKS). Ortho-McNeil Janssen Scientific Affairs, LLC, funded the study.

### About Bipolar Disorder

It is estimated that 27 million people worldwide(2) suffer from bipolar disorder, also known as manic-depressive disorder. It is

characterized by debilitating mood swings, from extreme highs (mania) to extreme lows (depression). Signs of mania include euphoria, extreme irritability or rage, accelerated or disorganized thinking and an increase in risky behaviors. Signs of depression include intense sadness or despair, loss of energy, insomnia and suicidal thoughts.

A classification of patients identified as "rapid-cycling" and also having four or more episodes during the previous 12 months, is estimated to occur in approximately 10-20% of patients with bipolar disorder seen in mood disorder clinics. The types of mood episodes (manic, depressed, mixed) seen in these patients can occur in any pattern. The course of their illness is characterized by a requirement for more health care resources, more concomitant medications and poorer outcomes.(4)

#### About Risperidone Long-Acting Injection

Risperidone long-acting injection is the first and only long-acting, atypical antipsychotic to be approved by the U.S. Food and Drug Administration and now is approved in more than 70 countries worldwide. The treatment uses Alkermes proprietary Medisorb(R) technology to deliver and maintain therapeutic medication levels in the body through just one injection every two weeks. Janssen markets Risperidone long-acting injection in the United States. The formulation is manufactured by Alkermes, Inc. (Nasdaq: ALKS). Available in 12.5 mg, 25 mg, 37.5 mg and 50 mg dose units, it is approved for the treatment of schizophrenia. For more information about RISPERDAL CONSTA, visit <http://www.risperdalconsta.com>.

Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., is based in Titusville, N.J. and is the only large pharmaceutical company in the U.S. dedicated solely to mental health. As the company celebrates its 50th year in mental health, it currently markets prescription medications for the treatment of schizophrenia, bipolar mania and the treatment of symptoms associated with autistic disorder. For more information about Janssen, visit <http://www.janssen.com>.

Alkermes, Inc. is a biotechnology company that uses proprietary technologies and know-how to create innovative medicines designed to yield better therapeutic outcomes for patients with serious disease. Alkermes manufactures RISPERDAL(R) CONSTA(R), marketed by Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. in the U.S. and Janssen-Cilag, a subsidiary of Johnson & Johnson, outside of the U.S. Alkermes also developed and manufactures VIVITROL(R), marketed in the U.S. primarily by Cephalon, Inc. The company's pipeline includes extended-release injectable, pulmonary and oral products for the treatment of prevalent, chronic diseases, such as central nervous system disorders, addiction and diabetes. Alkermes is headquartered in Cambridge, Massachusetts, with research and manufacturing facilities in Massachusetts and Ohio. For more information about Alkermes, visit <http://www.alkermes.com>.

(a) Stable remission was achieved if, during the last 4 weeks of the 16-week OL stabilization phase the subject had not met DSM-IV-TR criteria for active mood disorder; the subject had no crisis interventions; the subject's Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) total scores both remained less than or equal to 10 and the Clinical Global Impression -- bipolar severity (CGI-BP-S) score remained less than or equal to 3 and the subject's medications and doses of other psychotropic medications remained unchanged.

(b) RMB = a fully independent, blinded, international board of 3 psychiatrists considered experts in the treatment of bipolar disorder. They reviewed all clinical data and determined whether the patient met relapse criteria.

#### References

(1) Aphs L, Kujawa M, Macfadden W et al., Frequently relapsing bipolar disorder: evidence for an effective treatment using adjunctive risperidone long-acting injectable, presented at the 14th Biennial Winter Workshop on Schizophrenia, Montreux, Switzerland, February 2008.

(2) The Global Burden of Disease. World Health Organization, 2003. Available at [http://www.who.int/mip/2003/other\\_documents/en/globalburdenofdisease.pdf](http://www.who.int/mip/2003/other_documents/en/globalburdenofdisease.pdf), accessed January 18, 2008

(3) DSM-IV-TR, American Psychiatric Association, 2000.

(4) DSM-IV, American Psychiatric Association, 2000.

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