Investigational Agent Targeting Metabotropic Glutamate 2/3 Receptors Demonstrates Antipsychotic Activity in Humans, Study in Nature Medicine Finds

New approach for treatment of schizophrenia

INDIANAPOLIS, Sept 02, 2007 /PRNewswire-FirstCall via COMTEX News Network/ --

An investigational, phase II study published in the scientific journal Nature Medicine demonstrates that for the first time in humans a drug that acts on certain proteins in the brain called mGlu2/3 has antipsychotic activity. The study was sponsored by Eli Lilly and Company (NYSE: LLY).

In this study - a randomized, double-blind, placebo-controlled clinical trial - patients were assigned to four weeks of treatment with either Lilly's investigational compound LY2140023; olanzapine, an atypical antipsychotic medication that targets dopamine and serotonin receptors as an active control; or placebo. The study demonstrated that:

- LY2140023 and olanzapine showed statistically significant improvement versus placebo in PANSS (Positive and Negative Syndrome Scale), the most common scale used for measuring symptoms of patients with schizophrenia. Both groups showed a rapid response, within one week.
- Treatment with LY2140023 was not observed to have certain adverse events that often occur with currently approved schizophrenia medications, including increased prolactin elevations, extrapyramidal symptoms (involuntary movements or muscle stiffness), or weight gain.
- Overall, LY2140023 40 mg given twice daily was found to be safe and well-tolerated, with most adverse events being mild-to-moderate in severity and not treatment-limiting.

"These data provide compelling new evidence that mGlu2/3 receptor agonists have antipsychotic properties and may provide a completely new therapeutic approach for treating schizophrenia and, perhaps, other neuropsychiatric disorders," said Steven Paul, M.D., Lilly's executive vice president of science and technology. "Additional and longer-term studies are needed to confirm and extend these exciting initial findings. However, these data suggest that LY2140023 may provide a new alternative for the treatment of this often devastating condition."

Study Design

The trial was a proof of concept study designed to determine LY2140023 superiority versus placebo. Olanzapine was used as an active control. 196 patients with schizophrenia were randomly assigned to LY2140023 (40 mg twice daily), olanzapine (15 mg daily) or placebo. All participants were hospitalized to ensure patient safety, tapered off from any pre-trial antipsychotic medications (no therapeutically stable patients were included in the trial), and treated in a double-blind manner for four weeks. In all, 118 patients completed four weeks of the planned study treatment.

Results

Treatment with LY2140023 or olanzapine resulted in statistically significant improvement in PANSS (Positive and Negative Syndrome Scale) total score (primary outcome) compared to placebo (-20.8, $P < 0.001$; -26.7, $P < 0.001$; respectively), After four weeks of treatment, the study showed that both the LY2140023 group (32.0%, $P < 0.001$) and the olanzapine group (41.2%, $P < 0.001$) demonstrated significantly greater response rates compared to the placebo group (3.2%). Response was measured primarily by the PANSS, the most common scale used for measuring symptoms of patients with schizophrenia. A patient showing a 25% or more decrease in PANSS total score was defined as a responder. Additionally, a mean 0.51-kg weight reduction from baseline was observed in the LY2140023 group. A moderate but statistically significant weight gain was observed in the olanzapine group (0.74 kg, $P = 0.017$) relative to the placebo group.

Results showed that the placebo arm experienced the highest rate of study discontinuation due to lack of efficacy, however,

discontinuation due to adverse events was not significantly different across the three treatment groups (P = 0.66).

Adverse Events

Overall, the study showed that LY2140023 40mg, given twice daily, was found to be safe and well-tolerated, with most adverse events being mild to moderate in severity and not treatment-limiting. The most common treatment- emergent adverse events in the LY2140023 group were insomnia, affect lability (P = 0.038), nausea, headache, somnolence and blood creatine phosphokinase increase. The adverse event profile of LY2140023 did not include prolactin increase or worsening of extrapyramidal symptoms (EPS). Although mood lability seems to represent the most important potential adverse event, it should be noted that this outcome was observed primarily at one clinical site. In the olanzapine group, treatment-emergent adverse events included elevation in blood triglyceride levels (P = 0.005), insomnia, weight gain (P = 0.034), somnolence, akathisia, agitation and periodontitis (P = 0.03).

About LY2140023

LY2140023 is an investigational drug from Lilly, which is being developed as a new treatment option for schizophrenia. LY2140023 is an oral "prodrug," meaning it is devoid of intrinsic biological activity and, once administered, is metabolized to provide the active mGlu2/3 receptor agonist called LY404039. Most currently approved antipsychotic medications work by affecting the neurotransmitters dopamine or serotonin. For LY2140023, the active substance, LY404039, is thought to work by reducing the presynaptic release of another neurotransmitter, glutamate, in brain regions where mGlu2/3 receptors are expressed. Further studies are planned or are ongoing to learn more about the safety and effectiveness, including determining an optimal therapeutic dose for LY2140023.

About Olanzapine

Olanzapine is marketed by Lilly as Zyprexa. Zyprexa is indicated in the United States for the short- and long-term treatment of schizophrenia, acute mixed and manic episodes of bipolar I disorder, and maintenance treatment of bipolar disorder. Since Zyprexa was introduced in 1996, it has been prescribed to approximately 20 million people worldwide.

Zyprexa is not approved for the treatment of patients with dementia- related psychosis. Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with those patients taking a placebo. In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with Zyprexa.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Zyprexa.

As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with Zyprexa. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Also, as with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

The most common treatment-emergent adverse event associated with Zyprexa in placebo-controlled, short-term schizophrenia and bipolar mania trials was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, postural hypotension, dry mouth, asthenia, dyspepsia, increased appetite and tremor.

Full prescribing information, including a boxed warning, is available at www.zyprexa.com.

About Schizophrenia

Schizophrenia is a severe and debilitating psychosis often characterized by acute episodes of delusions (false beliefs that cannot be corrected by reason), hallucinations (usually in the form of non-existent voices) and long- term impairments such as diminished emotion, lack of interest and depressive signs and symptoms, such as hopelessness and suicidal thoughts.(1) It is usually associated with a disruption in social and family relationships. Schizophrenia is the most common severe mental illness. Twenty four million people suffer from schizophrenia worldwide. (2,3)

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

(Logo: http://www.newscom.com/cgi-bin/prnh/20031219/LLYLOGO)

C-LLY
Zyprexa(R) (olanzapine, Lilly)

(1) Weiden P, Scheifler P, Diamond R, et al. Breakthroughs in Antipsychotic Medications. New York: W.W. Norton & Company, 1999.
(2) The World Health Report 2001: Mental Health - New Understanding, New Hope. World Health Organization. Available at: http://www.who.int/whr/2001/chapter3/en/index1.html, accessed January 6, 2006.
(3) The Global Burden of Disease. World Health Organization in 2003. Available at: http://www.who.int/mip/2003/other_documents/en/globalburdenofdisease.pdf,

accessed January 6, 2006.

SOURCE Eli Lilly and Company