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Novel antipsychotic shows early promise

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07/11/13

HOLLYWOOD, FLA. – A novel oral antipsychotic, RP5063, displayed broad safety and efficacy for the treatment of schizophrenia and schizoaffective disorder in a phase II study.

RP5063 is a dopamine-serotonin system stabilizer. The agent is a potent partial agonist at the dopamine D2, D3, and D4 receptors and the serotonin 5-HT1A and 5-HT2A receptors, as well as an antagonist at the serotonin 5-HT6 and 5-HT7 receptors. Several of those sites have never been targeted by other medications, Dr. Marc Cantillon noted at a meeting of the New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health.

Sixty-one percent of the drug's metabolism is by the CYP3A4 pathway, the rest by the CYP2D6 pathway, an arrangement that provides a potential for low drug-drug interaction.

Dr. Marc Cantillon

The agent was designed to provide safe, less side effect laden, and more broadly effective alternatives to current atypical antipsychotics. RP5063 has minimal effects on off-target receptors, such as the histamine receptor, which are responsible for the common side effects of atypical antipsychotics that often result in poor treatment adherence, Dr. Cantillon explained.

He presented the results of the REFRESH trial, a 4-week, double-blind study of 234 patients with acute exacerbation of schizophrenia or schizoaffective disorder in the United States, Europe, and Asia. The patients were randomized 3:3:3:2:1 to once-daily RP5063 at 15, 30, or 50 mg/day, placebo, or aripiprazole (Abilify) at 15 mg/day.

Andreasen schizophrenia remission criteria (Am. J. Psychiatry 2005;162:441-9) were met by 34% of patients on RP5063 at 15 mg, 30% at 30 mg, and 46% at 50 mg, all significantly better than the 22% rate with placebo. The aripiprazole group was too small to include in the results comparison. Efficacy in the RP5063 group became significantly better than placebo within the first week and continued to steadily improve throughout the 4-week investigation, reported Dr. Cantillon, a psychiatrist and geriatrician in Livingston, N.J., and chief medical officer at Reviva Pharmaceuticals, which is developing RP5063.

Efficacy was defined as at least a 20% improvement over baseline on the Positive and Negative Syndrome Scale (PANSS) plus a 2-point improvement on the Clinical Global Impression Severity (CGI-S) scale; 46% of patients assigned to RP5063 at 15 mg/day met this bar, as did 32% of those on RP5063 at 30 mg/day and 33% on 50 mg/day, compared with 19% of placebo-treated controls.

"These remission efficacy levels within such a short study place RP5063 among the robust antipsychotics," Dr. Cantillon said.

While comparisons between different placebo-controlled randomized trials must be taken with a grain of salt, he said, the effect sizes for changes in PANSS scores with the three doses of RP5063 used in the REFRESH study are considerably bigger than in published meta-analyses of placebo-controlled trials of amisulpride, aripiprazole, quetiapine, olanzapine, or risperidone (Arch. Gen. Psychiatry 2003;60:553-64 and Mol. Psychiatry 2009;14:429-47).

On the safety front, 4 weeks of RP5063 resulted in no differences compared with placebo in terms of body weight, lipids, or blood glucose, suggesting the drug may produce fewer of the metabolic problems common of current atypical antipsychotics, noted Dr. Cantillon. Also, there were no significant differences between active treatment and control patients in terms of movement side effects or ECG changes. Serum prolactin levels declined by nearly 50% in all RP5063 treatment arms, then climbed back after the study ended.

Based upon the findings of REFRESH, a large phase III clinical trial of RP5063 for schizophrenia and schizoaffective disorder will start later this year.

"We'll probably be including a lower dose for use in pediatric and geriatric populations in phase III, since 15 mg performed so well in REFRESH," Dr. Cantillon said.

Because of its favorable balance of agonism and antagonism of key dopaminergic and serotonergic receptors and minimal off-target effects, RP5063 is also under development for the treatment of major depressive disorder, bipolar disorder, Tourette syndrome, autism, attention-deficit/hyperactivity disorder, and psychosis in Alzheimer's and Parkinson's disease.

The REFRESH trial was funded by Reviva Pharmaceuticals.

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