Drug Combo Leads to Significant Weight Loss

BY DOUG BRUNK

NEW ORLEANS — An investigational oral agent that combines naltrexone and bupropion produced clinically meaningful weight loss at 56 weeks, results from a multicenter phase III trial showed.

Bupropion is a norepinephrine-dopamine reuptake inhibitor that is approved for the treatment of depression and smoking cessation, while naltrexone is an opioid antagonist that is approved for alcohol and opioid dependence.

The investigational agent, known as Contrave (Orexigen Therapeutics Inc., San Diego), combines the two drugs and targets hunger, fullness, and reward centers in the brain that control the balance of food intake and energy expenditure,

Patients in the treatment group lost 9.3% of their body weight, compared with a 5.1% loss in the placebo group.

DR. WADDEN

Thomas A. Wadden, Ph.D., said at the annual scientific sessions of the American Diabetes Association.

Pending results from three additional phase III clinical trials expected to be announced in late 2009, Orexigen is on track to submit a New Drug Application to the Food and Drug Administration in the first half of 2010.

Dr. Wadden, a psychologist who directs the Center for Weight and Eating Disorders at the University of Pennsylvania, Philadelphia, and his coinvestigators enrolled 793 patients with a body mass index between 27 kg/m^2 and 45 kg/m^2 at nine sites in the United States. They studied the safety and efficacy of naltrexone/bupropion in patients who received intensive behavioral modification in the form of 28 group sessions that provided diet and exercise counseling.

Of the 793 patients, 591 were randomized to the study drug, which consisted of 32 mg of naltrexone and 360 mg bupropion per day, while 202 were randomized to placebo. The coprimary end points were percentage change in body weight and the proportion of patients who achieved a 5% loss of weight.

The mean age of patients was 46 years, 90% were female, 70% were white, and their mean BMI was 37 kg/m^2.

Overall, 460 patients (58%) completed the study. At 56 weeks, a modified intent-to-treat analysis showed that patients in the treatment group lost 9.3% of their body weight, compared with a loss of 5.1% in the placebo patients, a statistically significant difference.

In addition, significantly more patients in the treatment group than in the placebo group achieved a weight loss of 5% or more (66% vs. 42%, respectively). A similar pattern was seen for those who achieved a weight loss of 15% or more (29% vs. 11%).

The overall discontinuation rate due to adverse events was 26% in the treatment group, compared with 13% in the placebo group. The most frequent adverse events were nausea (34% in the treatment group vs. 11% in the placebo group), headache (24% vs. 18%), and constipation (24% vs. 14%).

"Nausea had a fairly rapid onset in participants, was generally mild or moderate, and tended to resolve in the first 4 weeks, and in most patients by 12 weeks," noted Dr. Wadden, professor of psychology in psychiatry at the University of Pennsylvania. "But there were some isolated cases that went further out."

The most frequent psychiatric adverse events reported were insomnia (9% in the treatment group vs. 6% in the placebo group), anxiety (5% vs. 4%), sleep disorder (2% vs. 3%), and depressed mood (2% vs. 4%).

Two serious cases of cholecystitis occurred in the treatment group and were believed to be triggered by rapid and significant loss of body weight.

Dr. Wadden disclosed that he is adviser to Orexigen Therapeutics Inc., which funded the study, as well as to Merck & Co., Novo Nordisk Inc., and Vivus Inc. ■