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NEW DRUG TREATS MULTIPLE PROBLEMS OF PEOPLE WITH TYPE 2 DIABETES

Rimonabant Lowers Blood Glucose and Reduces Weight, Waist Size, and Lipid Problems

San Diego, CA (June 12, 2005) – A novel drug has demonstrated that it can help multiple problems associated with type 2 diabetes by lowering blood glucose and reducing weight and waist circumference, as well as modifying the disordered lipids associated with diabetic dyslipidemia, according to a report presented today at the American Diabetes Association's 65th Annual Scientific Sessions.

“Results of the RIO-Diabetes (Rimonabant In Obesity) study show impressive findings in all aspects of the trial – especially in glycemic control and improvement in the lipid profile, in part explained by weight loss and in part independent of weight loss, suggesting that rimonabant may exert direct metabolic effects in type 2 diabetes,” said André Scheen, MD, PhD, professor of medicine and clinical pharmacology and head of the division of diabetes, nutrition and metabolic disorders, University of Liège, Belgium, in a recent interview. Over one year, those on 20 mg. rimonabant lowered A1C by 0.6 percent, lost 11.7 lbs and 2.05" in waist circumference, increased HDL 6.6 mg/dl, and lowered triglycerides 31.6 mg/dl – all significant differences (p values <0.001) from the placebo group.

Rimonabant is a selective CB₁ receptor endocannabinoid blocker, developed for managing cardiovascular risk factors, including intra-abdominal adiposity and its metabolic consequences. It is believed to act in two places: in the brain, where it reduces hunger, hence promoting weight loss; and in adipose (fat) tissue, where it increases levels of adiponectin, a cytokine (protein) secreted by such fat tissue. These proteins are decreased in obese individuals, a reduction that is associated with increased insulin resistance and a higher risk of developing type 2. It has been demonstrated in both animal models and human studies that when rimonabant increases adiponectin, insulin sensitivity is enhanced and diabetic dyslipidemia is improved.

- more -

RIO-Diabetes Study – Page 2

More than 18 million Americans have diabetes, a group of serious diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin. Diabetes can lead to severely debilitating or fatal complications, such as heart disease, blindness, kidney disease, and amputations. It is the fifth leading cause of death by disease in the U.S. Type 2 diabetes involves insulin resistance – the body's inability to properly use its own insulin. It usually occurs in those who are over 45 and overweight, but it has increasingly been seen in obese children and teens in recent years.

BACKGROUND

Intra-abdominal adiposity (belly fat), as measured by waist circumference, is associated with the development of insulin resistance and type 2 diabetes. As the prevalence of overweight and obesity continues to rise in our society, new therapeutic options are needed that address multiple factors, particularly promoting weight loss, lowering glucose levels, and modifying the lipid profile.

Diabetic dyslipidemia refers to a syndrome characterized by a cluster of abnormalities including: elevated triglycerides, reduced levels of HDL “good” cholesterol, and a shift toward smaller and denser LDL-cholesterol “bad” particles, although total and LDL levels may be normal *or* elevated.

In RIO-Europe and RIO-North America, both two-year trials in obese participants without diabetes, it has already been demonstrated that rimonabant 20 mg significantly increased weight loss, decreased waist circumference, reduced triglycerides, and increased HDL levels. In RIO-Lipids, a one-year trial in obese subjects with dyslipidemia, results were remarkably concordant.

- more -

RIO-Diabetes Study – Page 3

RIO-DIABETES

RIO-Diabetes, the study presented today, was a multicenter, randomized, double-blind, placebo-controlled, one-year-study. The 1,045 participants were 51 percent male, mean age 56 years, mean BMI 34, mean waist circumference 43.3", and mean A1C 7.5 percent.

Study participants had type 2 diabetes and had been treated with the biguanide metformin (two-thirds of patients) or one of several sulfonylureas for six or more months at the time of entry into the trial. All continued on these anti-diabetic drugs throughout the trial but also were randomized to receive placebo or rimonabant 5 mg. or 20 mg. once daily in a 1:1:1 ratio. A hypocaloric diet also was prescribed.

ONE-YEAR RESULTS

Dr. Scheen reported intention-to-treat results. (The differences in results for those on placebo vs. 5 mg. rimonabant were so minor, i.e. weight loss -3.1 lbs. vs. -5.1 lbs., that only placebo vs. 20 mg. rimonabant are reported here.) Thus, the results reported here include the 348 placebo participants and the 339 on 20 mg., who both averaged 212 lbs. at the outset.

The placebo group **weight loss** was -3.1 lbs. vs. -11.7 lbs. for the rimonabant group. The mean difference between placebo and 20 mg. rimonabant was 8.6 lbs. The proportion of patients who had at least a 5 percent body weight loss in one year was 14.5 percent on placebo and 49.4 percent on rimonabant 20 mg.

Changes in **waist circumference** paralleled weight loss. There was a 1.3" average difference in the loss between placebo and 20 mg. rimonabant. The researchers found that 2.2 lbs. of weight loss corresponded to a 0.4" reduction in waist circumference.

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RIO-Diabetes Study – Page 4

“The rimonabant trial was successful in its primary endpoint because we demonstrated that rimonabant promotes weight loss in people with diabetes,” said Dr. Scheen. “It is always difficult to compare with other compounds because we don’t have head-to-head studies in obesity, but these rimonabant results are at least as good as those with Orlistat or Sibutramine – the only two compounds widely used for obesity – and probably are slightly better.”

Further, he noted that a significant contribution by rimonabant is that participants reduced their abdominal obesity, as expressed in the decrease in waist circumference.

“Because we know that abdominal obesity is closely linked to insulin resistance, the metabolic syndrome and cardiovascular risk factors, if we target abdominal obesity we should expect a significant metabolic improvement, and indeed that is what we observed in this rimonabant study,” noted Dr. Scheen.

BLOOD GLUCOSE LEVELS

Hemoglobin A1C rose by 0.1 percent in the placebo group and dropped by 0.6 percent in the rimonabant 20 mg. group, a difference of 0.7 percent. The percentage of patients reaching the American Diabetes Association recommended treatment target of below 7 percent A1C after 1 year was 26.8 percent on placebo vs. 52.7 percent on rimonabant 20 mg. There was no difference between the metformin and sulfonylurea drug groups.

Treating physicians had the option to change doses of the underlying anti-diabetic to maintain glucose control. In the placebo group, there was a trend toward increasing the dose of metformin or sulfonylurea over the year of the study, while in the rimonabant 20 mg. group, more patients decreased the dose. However, 75 percent had no change in their anti-diabetic treatment.

- more -

RIO-Diabetes Study – Page 5

In order to discern whether the reduction in A1C could be explained by weight loss, statistical analysis was performed comparing the same weight loss in the placebo and rimonabant groups. It was determined that -0.3 percent of A1C was explained by weight loss and that -0.4 percent of A1C could not be explained by weight loss and is thus an independent effect.

CHANGES IN LIPID PROFILE

HDL rose 2.7 mg/dl in those on placebo vs. 6.6 mg/dl in those on rimonabant 20 mg., yielding an 8.4 percent difference.

Triglycerides rose 3.6 mg/dl in those on placebo vs. a decline of 31.2 mg/dl in those on rimonabant 20 mg., a difference of 16.4 percent.

“Again, in this and in all of the prior RIO studies, statistical analysis showed that part of the effect on lipid modification was due to the weight loss, and part due to the drug,” explained Dr. Scheen.

The **total/HDL ratio** was significantly decreased by rimonabant compared to placebo and the **non-HDL cholesterol** was significantly reduced by rimonabant compared to placebo. No significant effect was seen on **LDL** cholesterol, which is not surprising since it is not part of insulin resistance.

METABOLIC SYNDROME

Finally, the researchers looked at the metabolic syndrome, a cluster of risk factors that collectively increase the risk of cardiovascular disease. The study used the National Cholesterol Education Program Adult Treatment Panel III’s definition of the syndrome as three out of five of elements based on waist circumference, fasting plasma glucose, HDL, triglycerides, and blood pressure.

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RIO-Diabetes Study – Page 6

They found that of the 79 percent of patients who had metabolic syndrome at study entry, 73 percent on placebo, compared to only 64 percent on rimonabant 20 mg., still had the syndrome at the end of the year.

Contributing to that effect was a small decline of 0.8 mmHg in systolic blood pressure in the rimonabant 20 mg. group vs. a 1.6 mmHg increase in the placebo group. The difference in diastolic blood pressure between the two groups was not statistically significant.

SAFETY

The most common side effects were nausea and vomiting, which led to discontinuation in 1.5 percent of the rimonabant 20 mg. group, compared to 0.3 percent of the placebo group. Other side effects included minor anxiety and depressed mood disorders, leading to discontinuation rate of 3.3 percent in the rimonabant 20 mg. group, compared to 0.9 percent in the placebo group. Most side effects occurred within the first few weeks and tended to disappear in subsequent weeks.

THE FUTURE

Rimonabant is under development by sanofi-aventis with the brand name Acomplia. A new drug application is expected to be filed with the U.S. Food and Drug Administration in the near future.

The American Diabetes Association is the nation's leading voluntary health organization supporting diabetes research, information and advocacy. Founded in 1940, the Association has offices in every region of the country, providing services to hundreds of communities. For more information, please call the American Diabetes Association at 1-800-DIABETES (1-800-342-2383) or visit www.diabetes.org. Information from both these sources is available in English and Spanish.

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