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NEW STUDY SHOWS THAT EXPERIMENTAL WEIGHT LOSS DRUG MAY SLOW THE PROGRESSION OF HEART DISEASE

Chicago, IL –While studies have shown a correlation between abdominal obesity and heart disease, no clinical trials have demonstrated a benefit for weight management drugs in coronary disease patients. The Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant - The Intravascular Ultrasound Study (STRADAVARIUS), presented today at the American College of Cardiology’s 57th Annual Scientific Session, suggests that treatment with rimonabant may slow the progression of coronary disease in abdominally obese patients. ACC.08 is the premier cardiovascular medical meeting, bringing together cardiologists and cardiovascular specialists to further breakthroughs in cardiovascular medicine.

Rimonabant is an experimental agent not yet approved in the United States, but is available in some European countries. This drug represents the first of a new class of drugs that work by inhibiting cannabinoid type 1 (CB₁) receptors. These receptors are stimulated when people smoke marijuana, causing a ravenous appetite commonly known as the “munchies.” Blocking CB₁ receptors result in reduced food intake, an increase in HDL (“good”) cholesterol, and reductions in triglycerides and C-reactive protein (CRP).

Patients experience sustained decreases in body weight and reductions in waist circumference. Since atherosclerosis progression is accelerated by risk factors such as elevated LDL (“bad”) cholesterol and triglycerides, lower levels of HDL, high systolic blood pressure and diabetes, investigators sought to examine if rimonabant could slow the progression of coronary atherosclerosis in abdominally obese patients with the metabolic syndrome and preexisting coronary disease.

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Metabolic syndrome was defined as two or more of the following risk factors: triglyceride level >150 mg/dL, HDL-C < 40 mg/dL (men) or 50 mg/dL (women), a fasting plasma glucose >110 mg/dL, or high blood pressure (BP) defined as \geq 140/90 mm Hg or currently taking anti-hypertensive medications.

The STRADIVARIUS Trial randomized 839 patients at 112 centers in North America, Europe and Australia to receive either rimonabant or placebo and measured progression of disease by intravascular ultrasound, a technique that directly measures plaque buildup in the coronary arteries. Patients treated with rimonabant lost about 9.5 pounds and 1.8 inches in waist circumference. HDL cholesterol rose 22.4 percent, triglycerides decreased 20 percent and CRP levels decreased 50 percent. The primary endpoint, a calculation of disease burden known as Percent Atheroma Volume, did not show a statistically significant effect, but the secondary endpoint, the Total Atheroma Volume did show a statistically significant effect, p 0.03. The success or failure of a clinical trial is judged by the primary endpoint. Therefore, the study failed to meet its principal objective. However, the positive results for the secondary endpoint suggest that this approach has the potential to reduce plaque buildup in the coronaries, which will need to be confirmed in further trials.

An advisory panel of the U.S. Food and Drug Administration did not recommend approval of rimonabant in 2007 pending additional safety data. Therefore, the STRADIVARIUS investigators carefully assessed drug-related adverse effects in this trial. There was a statistically significant increase in psychiatric and gastrointestinal adverse effects, particularly anxiety, depression and nausea in patients randomized to rimonabant. A single patient in the placebo group attempted suicide and a single patient in the rimonabant group completed suicide. "Theoretically, a reduction in body weight with improvement in risk factors may slow the progression of coronary atherosclerosis," said Steven Nissen, M.D., Chairman, Department of Cardiovascular Medicine, Cleveland Clinic and lead author of the study. "Although the current study did not achieve a statistically significant effect for the primary efficacy measure, the favorable results for the secondary endpoint suggests that this approach to the treatment of abdominal obesity holds promise for patients with abdominal obesity and heart disease."

This study will be simultaneously published in the *Journal of the American Medical Association (JAMA)* and will appear in the April 2 print edition and be released online at the time of presentation.

Dr. Nissen will present "Effect of Rimonabant on Progression of Atherosclerosis in Patients With Abdominal Obesity and Coronary Artery Disease" at the ACC.08 Late-Breaking Clinical Trials II session on Tuesday, April 01, 2008, 10:00 am - 11:30 am, McCormick Place, North Hall B1.

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The American College of Cardiology (www.acc.org) represents the majority of board certified cardiovascular physicians in the United States. Its mission is to advocate for

quality cardiovascular care through education, research, promotion, development and application of standards and guidelines – and to influence health care policy. ACC.08 is the largest cardiovascular meeting, bringing together cardiologists and cardiovascular specialists to share the newest discoveries in the treatment and prevention, while helping the ACC achieve its mission to address and improve issues in cardiovascular medicine.