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DESPITE SIGNIFICANTLY RAISING HDL, TORCETRAPIB FAILED TO SLOW THE PROGRESSION OF CORONARY PLAQUES

NEW ORLEANS, La. (March 26, 2007) — Investigators reported today that torcetrapib, a drug that substantially raises high-density lipoprotein cholesterol or HDL (the “good” cholesterol), did not slow the progression of plaque buildup in the coronary arteries as measured using an ultrasound probe (IVUS). All development of this drug was terminated on December 2, 2006 after the safety board monitoring a separate large clinical outcomes trial reported that torcetrapib increased the risk of death and other adverse cardiovascular outcomes.

The results of the study presented today at the American College of Cardiology’s 56th Annual Scientific Session are considered pivotal in determining whether the failure of torcetrapib was the result of specific drug toxicity or a failure of the entire approach as a means to raise HDL. ACC.07 is the premier cardiovascular medical meeting, bringing together cardiologists and cardiovascular specialists to further breakthroughs in cardiovascular medicine. This study will be simultaneously published in the *New England Journal of Medicine* and will appear in the March 29 print issue. The development of drugs to raise HDL has been a research priority because, despite lowering LDL (low-density lipoprotein, or “bad”) cholesterol with statin drugs, many patients continue to experience heart attacks, stroke or sudden cardiac death.

A total of 1,188 coronary artery disease patients were enrolled in a trial called ILLUSTRATE (Investigation of Lipid Level management using coronary UltraSound To assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). All patients had a clinical indication for cardiac

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2 – 2 – 2 ILLUSTRATE (Torcetrapib)

catheterization, had a baseline intravascular ultrasound (IVUS), and received 10-80 gm of atorvastatin adjusted during a two- to 10-week period until LDL levels reached national guidelines. Patients were then randomized to receive either 60 mg of torcetrapib or a matching placebo for two years. At the end of the treatment period, a second IVUS was performed, examining the same coronary arteries. Researchers measured the change in plaque volume in the artery, comparing the baseline to the follow-up ultrasound, and measured patients' blood cholesterol levels and biomarkers of inflammation at several points during the trial.

Patients in the torcetrapib/atorvastatin group experienced a 61 percent relative increase in HDL cholesterol levels and a 20 percent relative decrease in LDL levels, as compared with patients in the atorvastatin-only group. Despite those results, there was no statistical difference between the two groups in plaque volume changes. Plaque volume increased by 0.19 percent in the atorvastatin-only patients and 0.12 percent in the combination group, $p = 0.72$. Torcetrapib was associated with a substantial increase in blood pressure. During the course of the study, the torcetrapib-treated patients had a systolic BP that averaged 4.6 mm Hg greater than the atorvastatin-only patients. Furthermore, torcetrapib patients were more than twice as likely to increase systolic BP more than 15 mmHg compared with atorvastatin alone.

"The torcetrapib/atorvastatin combination markedly increased good cholesterol levels and lowered bad cholesterol. Yet this drug substantially raised blood pressure, an undesirable effect, and failed to slow the build up of plaque," said Steven Nissen, M.D., of the Cleveland Clinic and lead author of the study. Dr. Nissen is also President of the American College of Cardiology. "Whether this failure represents a problem unique to torcetrapib or suggests a lack of efficacy for the entire class of similar drugs remains to be determined. Our findings demonstrate the great difficulty in developing therapies to interrupt the atherosclerosis process. Twenty years after the introduction of statins, we are still waiting for the next breakthrough."

IVUS is a technique in which a tiny ultrasound probe is inserted into the coronary arteries, providing a precise, reproducible method to determine changes in plaque, or atheroma, during treatment.

Dr. Nissen will present the results of the "Effect of Torcetrapib on the Progression of Coronary Atherosclerosis" study on Monday, March 26 at 8:30 a.m. in Hall A.

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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.07 and the i2 Summit is the largest cardiovascular meeting, bringing together cardiologists and cardiovascular specialists to share the newest discoveries in treatment and prevention, while helping the ACC achieve its mission to address and improve issues in cardiovascular medicine.