May 26, 2011 -- Bale/Doneen Response to the Halt of the AIM-HIGH Study

NHLBI announced that the AIM-HIGH study has been stopped. AIM-HIGH, a randomized, multicenter clinical trial sponsored by the NHLBI was designed to answer the question of whether raising high-density lipoprotein cholesterol (HDL-C) in patients with a history of stable, non-acute pre-existing cardiovascular disease and well controlled low-density lipoprotein cholesterol (LDL-C) would lower the rate of CV events.

All AIM-HIGH participants were treated with simvastatin, with the possible addition of ezetimibe, to achieve an LDL-C between 40 and 80 mg/dL. Patients were randomly assigned to also receive either Niaspan or placebo.

The AIM-HIGH data and safety monitoring board recommended stopping the trial as of May 25, 2011 because of lack of efficacy. The data from the interim analysis indicated that the trial does not show a significant difference in cardiovascular outcome event rates between the two study arms. There were 249 primary outcome events (15%) in the simvastatin arm and 262 (15%) in the Niaspan plus simvastatin (p=0.561). There were a total of 28 ischemic strokes (1.6%) in the Niaspan plus simvastatin arm and a total of 12 such events (0.7%) reported in the simvastatin arm.

**Bale/Doneen Method thoughts:**

This AIM-HIGH announcement and trial cessation allows the opportunity to propose several relevant and important questions. We must recognize that AIM-HIGH was slated to validate many of our observations of previous clinical trials and certain clinical observations. The NHLBI’s decision to halt this trial is based on a lack of efficacy, not an increase risk for clinical events. Regardless, we await the full disclosure with much anticipation. In the meantime, we are left to search for potential meaning of these preliminary findings, knowing that the full release will hopefully provide the needed information to formulate a clinical decision for our patients. We have listed several thoughts below that detail our current thoughts on the early release. We, like you, anticipate the full release by the AIM-HIGH study investigators to fully appreciate the depth and limitation of this complicated issue. The highlighted areas of discussion below represent our thoughts today, which will surely reformulate as further data is released.

**Intent to treat:** AIM HIGH was designed as an "intent to treat" study, which allows for individuals to be included in the treatment arm without daily compliance monitoring of medication adherence. Nine of the ischemic stroke events reported in the Niaspan arm occurred after the subjects had stopped taking Niaspan for 67-1467 days. Niaspan administration requires careful monitoring to insure compliance with treatment therapy. As we know, if the medication is not taken daily, its treatment benefit is negated.
**Confounding therapies:** Ezetimibe was used in 515 participants as an add-on therapy to the statin therapy with the intent to get LDL to the treated goal of 40-80. It remains yet unclear how many participants in the Niacin/statin ischemic stroke arm were also taking ezetimibe. The potential interaction between Niaspan and ezetimibe has never been formally evaluated. We do know from the ENHANCE trial and ARBITER 6, that ezetimibe is an effective add-on to statin therapy to lower LDL. It has been determined, however, that the addition of ezetimibe to a statin falls short of improving atherosclerosis, as measured by carotid intima-media thickness. We also do not know the potential relationship of ezetimibe and Niaspan – this remains unclear.

**Population:** Inclusion criteria for the study subjects included established cardiovascular disease and atherogenic dyslipidemia. This demographic possesses a multi-factorial treatment challenge, often including obesity, hypertension, insulin resistance and metabolic syndrome. This study was designed to treat the lipid portion of this risk factor profile. In this difficult to treat population, therapy beyond the lipids is essential. Treatment issues include blood pressure management, psychosocial management, exercise support, diet support, sleep management and optimal treatment of insulin resistance. Clearly, this trial perhaps supports the opportunity to recognize the multi-factorial treatment necessary to treat stroke risk in this complicated patient population.

**Stroke Prevention:** The INTERSTROKE trial provides the best insight into the most common causes of ischemic stroke. The most common cause of ischemic stroke, worldwide, was determined to be blood pressure. We do not know how well BP was controlled in these patients.

**Heart Attack Prevention:** The INTERHEART trial looked at a worldwide population and it was determined that lipids were the number one risk factor for heart attacks. AIM-HIGH is a lipid trial and, according to the preliminary release, heart attack concerns were not raised by the NHLBI safety board.

**Arterial Inflammation:** Events are triggered by inflammation. Eradication of arterial inflammation in individuals who are resistant to insulin frequently requires therapy beyond statin and niacin. It will be interesting to see the trial results in regards to biomarkers of inflammation.

The story is yet to unfold and we will be watching the daily press releases with the intent to determine the true reason for this rather surprising announcement. We share the same concerns as many providers who are dedicated to the prevention of heart attacks, ischemic stroke and diabetes. The story will continue....

Respectfully,

Amy Doneen and Bradley Bale