



**Subject: Updated Information from Cardiovascular prevention trial, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)**

November 15, 2011

Dear Healthcare Professional:

On May 26, 2011, Abbott sent you information regarding an interim analysis of the AIM-HIGH study which investigated NIASPAN<sup>®</sup> (niacin extended-release tablets) in combination with simvastatin versus simvastatin. The final study results were announced today at the American Heart Association Scientific Sessions 2011 and published in the *New England Journal of Medicine*. We would like to inform you of the final results of the AIM-HIGH Study.

### Summary

- The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial was a five-year multicenter, prospective, randomized, double-blind, parallel-group, active comparator study of 3414 randomized patients that evaluated whether adding NIASPAN to statin therapy in patients with stable, non-acute, pre-existing cardiovascular (CV) disease with well-controlled LDL-C (40 – 80 mg/dL) would provide an additional 25% reduction in CV events on top of the reductions observed for statins.<sup>1</sup> Prior clinical trials have found a 25% to 35% CV risk reduction using statin monotherapy.
- On May 26, 2011, the NHLBI (National Heart, Lung, and Blood Institute) announced, based on interim results, that the AIM-HIGH study was stopped early due to futility. The interim analysis concluded that the study objective could not be met; the combination of NIASPAN and simvastatin did not result in an additional reduction in CV events, beyond that occurring with simvastatin, in the well-controlled population tested.

- Final study results reveal that the primary endpoint occurred in 282 NIASPAN plus simvastatin patients (16.4%) and in 274 simvastatin patients (16.2%), a non-statistically significant difference; HR: 1.02; 95% CI: 0.87, 1.21,  $P=0.80$ . The primary endpoint was the composite time to first occurrence of coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for ACS, or symptom driven coronary or cerebral revascularization.
- 94% of the AIM-HIGH patients were already on statins at randomization, and most of these patients were well-treated with statins for years prior to entering the study: 76% were on statins for at least one year and 40% for 5 or more years. These patients had median baseline LDL-C of 71 mg/dL, non-HDL-C of 106 mg/dL, TG of 161 mg/dL, HDL-C of 35 mg/dL and Apo B of 80 mg/dL. For the 6% of the patients not taking a statin at study entry, median baseline LDL-C was 125 mg/dL, non-HDL-C was 166 mg/dL, TG were 215 mg/dL, HDL-C was 33 mg/dL and Apo B was 108 mg/dL.
- Therefore, the majority of patients were near the NCEP ATP III guideline optional goal for very high-risk CV patients of LDL-C of <70 mg/dL and non-HDL-C target of <100 mg/dL (LDL-C + 30 mg/dL); thus, NCEP would not recommend further lipid modification for patients in this study population.
- NIASPAN use resulted in statistically significant increases in HDL-C at year 2 and decreases in TGs, LDL-C, and non-HDL-C, consistent with the known effects of the drug.
- The AIM-HIGH findings should be applied only to the type of patient enrolled in that trial. The clinical significance of these findings in other patient populations is unknown.
- A retrospective analysis of three large independent claims and epidemiology databases with data from 2003 through 2010 indicated that the AIM-HIGH study population does not represent the typical patient seen in the clinical setting. In contrast to the randomized AIM-HIGH population, this analysis showed that 20-26% of the high-risk, statin-treated patient population reached baseline LDL-C levels of <70 mg/dL and 13-19% reached both the baseline LDL-C and non-HDL-C levels.<sup>2</sup>
- Based on the interim data, there was an imbalance in ischemic stroke in the NIASPAN plus simvastatin arm versus the simvastatin arm that contributed to the AIM-HIGH data safety monitoring board's (DSMB) recommendation to stop the study 18 months prior to its planned conclusion.
- Based on the final data, the difference in the total ischemic stroke events between the two study arms is not statistically significant (n=29 versus n=18 in the NIASPAN plus simvastatin arm compared to the simvastatin arm for all ischemic stroke events;  $P=0.11$ ).
- Eight of these patients, in the NIASPAN plus simvastatin arm, developed ischemic stroke after discontinuation of study drug (range of 2 months to 4 years after the last dose of study drug). When these events are removed, the difference between the 2 study arms is further decreased (n=21 in the NIASPAN plus simvastatin versus n=18 in the simvastatin arm).

- Analyses of previous clinical studies have not shown that stroke is a potential complication of NIASPAN and niacin in any therapeutic formulation, dose, or dosing regimen. Subsequent to the release of the interim AIM-HIGH results, Abbott conducted a thorough analysis of previous NIASPAN clinical trials. This analysis also did not identify a stroke signal.
- Discontinuation of study drug in the AIM-HIGH Study occurred in 25% of subjects in the NIASPAN plus simvastatin arm compared with 20% of subjects in the simvastatin arm,  $P < 0.001$ . In the NIASPAN plus simvastatin arm, 6% of patients discontinued due to flushing.
- Reported adverse effects in the AIM-HIGH Study included liver function abnormalities (0.8% and 0.5% in the NIASPAN plus simvastatin and simvastatin arms, respectively), muscle symptoms/myopathy (0.3% of subjects overall), and rhabdomyolysis (4 NIASPAN plus simvastatin and 1 simvastatin patients). These events are consistent with the known NIASPAN safety profile.

The full article is available online at [www.nejm.org](http://www.nejm.org). This letter is also available at [www.NIASPAN.com](http://www.NIASPAN.com).

Abbott will review the final AIM-HIGH trial data with FDA to assess potential revisions to NIASPAN (niacin extended-release tablets) and/or SIMCOR (niacin extended-release/simvastatin) labeling.

Abbott is committed to ensuring that NIASPAN is used safely and effectively and to providing you with the most current product information for NIASPAN. You can assist us with monitoring the safety of NIASPAN by reporting adverse events to Abbott at 1-800-633-9110. Alternatively, this information may be reported to the FDA's MedWatch reporting system by: phone (1-800-FDA-1088), fax (1-800-FDA-0178), [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or mailed to: MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787.

Should you have any questions or require further information regarding the use of NIASPAN, please contact Abbott's Medical Information Department at 1-866-257-8292 or via the web at [www.abbottmedinfo.com](http://www.abbottmedinfo.com).

Sincerely,



Robert Hoff, M.D.  
Head Global Medical Communications

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and other nonpharmacological measures alone has been inadequate.

#### **INDICATIONS FOR NIASPAN<sup>®</sup> (niacin extended-release tablets)**

- NIASPAN is indicated to reduce elevated TC, LDL-C, Apo B, and TG levels, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia.
- NIASPAN in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate.
- **Limitations of Use:** No incremental benefit of NIASPAN coadministered with simvastatin or lovastatin on cardiovascular morbidity and mortality over and above that demonstrated for niacin, simvastatin, or lovastatin monotherapy has been established.

#### **INDICATIONS FOR SIMCOR<sup>®</sup> (niacin extended-release/simvastatin)**

- SIMCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, Apo B, non-HDL-C, or TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.
- SIMCOR is indicated to reduce TG in patients with hypertriglyceridemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.
- **Limitations of Use:** No incremental benefit of SIMCOR on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin monotherapy and niacin monotherapy has been established.

#### **IMPORTANT SAFETY INFORMATION for NIASPAN and SIMCOR**

- NIASPAN and SIMCOR are contraindicated in patients with active liver disease or unexplained persistent elevations in hepatic transaminases, active peptic ulcer disease, arterial bleeding, and hypersensitivity to any product ingredients. SIMCOR is also contraindicated in women who are pregnant or may become pregnant; in nursing mothers; and with concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone), gemfibrozil, cyclosporine, danazol, amiodarone, verapamil, or diltiazem.
- **Do not substitute NIASPAN or SIMCOR for equivalent doses of immediate-release (crystalline) niacin. Severe hepatic toxicity, including fulminant hepatic necrosis, can occur. Patients switching from immediate-release niacin to NIASPAN or SIMCOR should start with the lowest dose at bedtime and then be titrated to the desired therapeutic response.**

- **NIASPAN and SIMCOR should be used with caution in patients with renal disease, a past history of liver disease, and/or who consume substantial quantities of alcohol.**
- NIASPAN and SIMCOR can increase hepatic transaminases. Monitor liver enzymes before and during treatment and discontinue therapy if they show evidence of progression, particularly to 3X ULN and are persistent, or if levels are associated with symptoms of nausea, fever, and/or malaise. **The efficacy and safety of doses of SIMCOR >2000/40 mg daily have not been studied and are therefore not recommended.**
- Myopathy has been reported in patients taking NIASPAN. The risk for myopathy and rhabdomyolysis increases when a statin is coadministered with NIASPAN, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. Myopathy and/or rhabdomyolysis have been reported when a statin is used in combination with lipid-altering doses ( $\geq 1$  g/day) of niacin. Advise patients to promptly report unexplained muscle pain, tenderness, or weakness particularly during the initial months of therapy and during upward dosage titration of either drug. Periodic serum creatine phosphokinase (CPK) and potassium determinations should be considered in such situations. Discontinue NIASPAN or SIMCOR if myopathy is diagnosed or suspected.
- SIMCOR contains simvastatin, which occasionally causes myopathy manifested as muscle pain, tenderness, or weakness with CK levels above 10X ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Risks of myopathy increase with higher doses, concomitant use of certain medicines (e.g. ranolazine, amlodipine, and colchicine), and consuming large quantities of grapefruit juice (>1 quart daily). Predisposing factors include advanced age ( $\geq 65$ ), female gender, uncontrolled hypothyroidism, renal impairment, and Chinese ethnicity. **All patients starting therapy with SIMCOR, or whose dose of SIMCOR is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report symptoms promptly. SIMCOR should be discontinued immediately if myopathy is diagnosed or suspected.**
- Use NIASPAN with caution in patients with unstable angina or in the acute phase of an MI; renal impairment; a past history of jaundice, hepatobiliary disease, or peptic ulcer.
- NIASPAN and SIMCOR can increase serum glucose levels. Closely monitor glucose levels in diabetic or potentially diabetic patients, particularly during the first few months of use or during dose adjustment.
- NIASPAN and SIMCOR can reduce platelet counts and increase prothrombin time (PT); accordingly, carefully evaluate patients undergoing surgery. In patients taking anticoagulants, monitor PT, INR, and platelet counts before and during treatment. NIASPAN and SIMCOR can increase uric acid levels; use with caution in patients predisposed to gout.

- SIMCOR can decrease serum phosphorus. Transient but statistically significant decreases in serum phosphorus have also been reported with NIASPAN. Phosphorus levels should be monitored periodically in patients at risk for hypophosphatemia.
- Bile acid sequestrants should be taken at least 4-6 hours apart from NIASPAN administration.
- The most common adverse reaction with NIASPAN and SIMCOR is flushing (warmth, redness, itching, and/or tingling of the skin). Flushing may vary in severity and is more likely to occur with initiation of therapy or during dose increases. Advise patients of the symptoms of flushing and how they differ from the symptoms of an MI.
- Other common adverse reactions (incidence >5% and greater than placebo) for NIASPAN are diarrhea, nausea, vomiting, increased cough, and pruritus.
- Other common adverse reactions for SIMCOR (incidence  $\geq 3\%$ ) were headache, pruritus, nausea, back pain, and diarrhea.

Please visit <http://www.rxabbott.com/pdf/niaspan.pdf> for full Prescribing Information for NIASPAN.

Please visit [http://www.rxabbott.com/pdf/simcor\\_pi.pdf](http://www.rxabbott.com/pdf/simcor_pi.pdf) for full Prescribing Information for SIMCOR.

#### References:

1. The AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: Baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) trial. *Am Heart J.* 2011;161:538-543.
2. Data on File. Epidemiology of dyslipidemia – beyond LDL-C: GE Centricity, United Healthcare, National Health and Nutrition Examination Survey. Abbott. October 2011.