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News Release

EVOLVE Analysis Demonstrates Omega-3 Carboxylic Acids Significantly Reduce Plasma ApoCIII

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May 25, 2015, Amsterdam - The Harvard T.H. Chan School of Public Health is pleased to announce the results of a new analysis of the EVOLVE trial (**E**pano**V**a f**O**r **L**owering **V**ery high triglyceride**s**), which demonstrated that omega-3 carboxylic acids significantly reduce plasma apoCIII. The results were presented today in a Clinical Breakthrough Session at the 17th International Symposium on Atherosclerosis, Amsterdam, The Netherlands, which is being held May 23-26, 2015.

Lipoprotein subspecies containing apoCIII have been shown to adversely affect the risk of cardiovascular disease (CVD). Specifically, LDL with apoCIII is a stronger predictor of CVD than LDL without apoCIII[1,2], and HDL with apoCIII is also associated with increased CVD risk[3]. Small studies suggest omega-3 fatty acids may reduce total apoCIII in the blood plasma in addition to their triglyceride (TG)-lowering effects[4-6].

The EVOLVE trial was a 12-week double-blind study of 399 subjects with fasting TG levels between 500 and 2000 mg/dL randomized to 2,3 or 4 gram/day (g/d) doses of omega-3 carboxylic acids, or an olive oil placebo. The analysis conducted by the School of Public Health Ph.D. candidate Allyson Morton, Research Scientist Jeremy D. Furtado and Research Associate Jane Lee, examined the baseline and end of treatment plasma samples of 273 subjects randomized to 2 or 4 g/d to determine the effect of omega-3 carboxylic acids on apoCIII concentrations in HDL, LDL and VLDL, as well as on the concentrations of subspecies of HDL, LDL and VLDL that contain or do not contain apoCIII.

The results demonstrated omega-3 carboxylic acids significantly reduced plasma apoCIII as compared to placebo (-4.2 mg/dL, p=0.002 and -4.0 mg/dL, p<0.0001 for 2 and 4g, respectively), as well as apoCIII in HDL (-0.6 mg/DL, p=0.12 and -1.0 mg/dL, p=0.01 for 2 and 4g, respectively) and apoCIII in LDL (-2.9 mg/dL, p<0.0001 and -3.3 mg/dL, p<0.001 for 2 and 4g, respectively).

Omega-3 carboxylic acids selectively increased the concentration of LDL apoB, a subtype that does not contain apoCIII and has a weak correlation to coronary heart disease (5.1 mg/dL, p=0.047 and 7.1 mg/dL, p=0.006 for 2 and 4g, respectively). Treatment did not significantly increase the concentration of LDL with apoCIII (0.15 mg/dL, p=0.7 and 0.2 mg/dL, p=0.6 for 2 and 4g, respectively).

“These results are exciting because they contribute to the growing body of research that support triglyceride lowering as the next target in the treatment of cardiovascular disease. Furthermore, it is becoming evident that simple measurements of HDL-C and LDL-C, without investigating proteins that reside on these particles, do not adequately reflect lipoprotein function in the body and disease risk,” said Allyson Morton, Ph.D. candidate, Harvard T.H. Chan School of Public Health.

These results indicate that omega-3 carboxylic acids at doses of 2 and 4 g/d are effective for lowering total plasma apoCIII and apoCIII in HDL and LDL. Further, the increase in LDL

concentration seen with omega-3 carboxylic acids is limited to the less harmful subspecies of LDL without apoCIII. The authors concluded apoCIII may be a mechanism for the TG lowering effects of omega-3 carboxylic acids. Further studies are needed to determine whether omega-3 carboxylic acids reduces cardiovascular risk and whether this is related to apoCIII reduction.

Omega-3 carboxylic acids is marketed by AstraZeneca as EPANOVA® and contains EPA (50-60%) and DHA (15-25%) in free fatty acid form. Funding for the EVOLVE trial was originally provided by Omthera Pharmaceuticals, Inc.

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NOTES TO EDITORS

About EPANOVA

EPANOVA is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia in the US. EPANOVA is manufactured by AstraZeneca.

Important Safety Information for EPANOVA® (omega-3-carboxylic acids) Capsules

- EPANOVA is contraindicated in patients with known hypersensitivity to EPANOVA or any of its components
- In some patients, EPANOVA increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with EPANOVA. In patients with hepatic impairment, ALT and AST levels should be monitored periodically during therapy with EPANOVA
- EPANOVA should be used with caution in patients with known hypersensitivity to fish and/or shellfish

- Some published studies with omega-3-acids demonstrated prolongation of bleeding time, which did not exceed normal limits and did not produce clinically significant bleeding episodes. Patients taking anti-platelet agents or anticoagulants were excluded from EPANOVA clinical trials involving patients with hypertriglyceridemia. Nonetheless, patients receiving treatment with EPANOVA and an anticoagulant or other drugs affecting coagulation (eg, anti-platelet agents) should be monitored periodically

- Most common adverse reactions with EPANOVA 2 grams and 4 grams, respectively, were diarrhea (7%, 15%), nausea (4%, 6%), abdominal pain or discomfort (3%, 5%) and eructation (3%, 3%)

Please see full US Prescribing Information
http://www1.astrazeneca-us.com/pi/epanova.pdf

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving EPANOVA and should continue this diet during treatment with EPANOVA. Laboratory studies should be done to ascertain that the triglyceride levels are consistently abnormal before instituting EPANOVA therapy. Attempts should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use: The effect of EPANOVA on the risk for pancreatitis has not been determined. The effect of EPANOVA on cardiovascular mortality and morbidity in patients has not been determined.

http://www.epanovahcp.com/

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Harvard T.H. Chan School of Public Health brings together dedicated experts from many disciplines to educate new generations of global health leaders and produce powerful ideas that improve the lives and health of people everywhere. As a community of leading scientists, educators, and students, we work together to take innovative ideas from the laboratory to people's lives—not only making scientific breakthroughs, but also working to change individual behaviors, public policies, and health care practices. Each year, more than 400 faculty members at Harvard Chan teach 1,000-plus full-time students from around the world and train thousands more through online and executive education courses. Founded in 1913 as the Harvard-MIT School of Health Officers, the School is recognized as America's oldest professional training program in public health.

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