New Analysis Assesses Impact of Common Genetic Variation on Benefit of Antiplatelet Therapy

More than one out of four patients in analysis had variant in ABCB1 gene

PARSIPPANY, N.J. and INDIANAPOLIS, March 15, 2010 /PRNewswire via COMTEX News Network/ -- A new analysis of the TRITON-TIMI 38 study evaluated response rates in patients with a common genetic variant in the ABCB1 gene. Patients enrolled in the TRITON-TIMI 38 study were treated with dual antiplatelet therapy with either Plavix(R) (clopidogrel) plus aspirin or Effient(R) (prasugrel) plus aspirin and managed with percutaneous coronary intervention (PCI) following an acute coronary syndrome (ACS) event. The results of this retrospective genetic sub-study were presented today at the American College of Cardiology annual meeting.

The ABCB1 gene contains the genetic code for a protein (P-glycoprotein) that plays an important role in how the body absorbs many medications, including antiplatelet drugs. Genetic variants in ABCB1 may reduce response to antiplatelet therapy.

In this sub-study, the TRITON-TIMI 38 investigators analyzed clinical outcomes among 2,943 patients tested for the "C3435T" variant in the ABCB1 gene. More than one out of four (27 percent) patients in the analysis were found to have two C3435T variants in their chromosomes.(1) Clopidogrel-treated patients who had two C3435T variants (n=414) had a 66 percent increased risk of experiencing the primary composite endpoint of cardiovascular death, heart attack or stroke compared to clopidogrel-treated patients without the variant (12.9 percent vs. 8.2 percent, HR=1.66; p=0.033). The overall ABCB1 genetic analysis, which included clopidogrel patients with two, one or no C3435T variants, also showed a significant increase in the primary endpoint for patients with two variants (p=0.0064).

In contrast, Effient-treated patients with two C3435T variants (n=390) did not have a statistically significant increased risk of experiencing the primary composite endpoint compared to Effient-treated patients without the variant (11 percent vs. 9.7 percent, HR=1.12; p=0.64), and the differences in the overall ABCB1 analysis were likewise not significant (p=0.40).

"These data are important because they suggest that multiple genetic variations may impact a patient's response to antiplatelet medications, and that these effects appear to differ from medication to medication," said Jessica Mega, M.D., M.P.H., associate physician at Brigham and Women's Hospital and investigator at the TIMI Study Group. "Understanding the full scope of these genetic variations may help determine which drug to prescribe as part of the dual antiplatelet therapy a patient receives after an angioplasty with a stent."

In this subanalysis, there was no association between C3435T genotype and bleeding in either treatment group. In the overall TRITON-TIMI study population, Effient produced higher rates of clinically significant bleeding than clopidogrel.

Study Methodology

TRITON-TIMI 38 was a Phase III, randomized, double-blind, head-to-head clinical trial comparing the effects of Effient versus clopidogrel in patients with ACS who were managed with PCI, a procedure to open blockages in heart arteries, including the use of coronary stenting. The study enrolled 13,608 patients at 707 trial sites in 30 countries.

The primary endpoint of the study was the combined incidence of cardiovascular death, non-fatal heart attack or non-fatal stroke during a median period of at least 12 months following PCI. Patients were randomly assigned to one of two treatment groups and given a loading dose of either Effient 60 mg or the FDA-approved loading dose of clopidogrel 300 mg, followed by a daily maintenance dose of either Effient 10 mg or clopidogrel 75 mg. All patients also received a daily dose of aspirin (75 mg to 325 mg).

This analysis was designed to examine whether specific genetic variations could affect patient response to antiplatelet therapy. The pharmacogenetic analyses examined DNA samples from 2,943 patients from the TRITON-TIMI 38 clinical trial.

The genetic subanalysis was not powered to make efficacy comparisons between clopidogrel and prasugrel based on genetic variations.

About Effient

Daiichi Sankyo Company, Limited (TSE: 4568), and Eli Lilly and Company (NYSE: LLY) co-developed Effient, an oral antiplatelet agent discovered by Daiichi Sankyo and its Japanese research partner, Ube Industries, Ltd. Effient helps keep blood platelets from clumping together and developing a blockage in an artery. Effient is approved by the U.S. Food and Drug Administration for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are managed with an artery-opening procedure known as percutaneous coronary intervention (PCI). PCI usually includes the placement of a stent to help keep the artery open.

About Acute Coronary Syndromes

ACS, which includes heart attack and unstable angina (chest pain), affects more than 1.5 million people in the United States annually, many of whom are managed with PCI.(2) In 2009, an estimated 785,000 people in the United States will have a new heart attack, and about 470,000 will have a recurrent attack.(3) ACS results in significant morbidity and mortality, accounting for half of all deaths due to cardiovascular disease, and costs Americans more than $150 billion annually, nearly 60 percent of which results from rehospitalization.(4)

Important Safety Information about Effient

Antiplatelet medicines, including Effient, can increase a patient's risk of bleeding. If patients have unexplained or excessive bleeding while on Effient, they should contact their doctor right away as some bleeding can be serious, and sometimes may lead to death. Patients should not take Effient if they have a stomach ulcer or other conditions that cause bleeding or if they have a history of stroke or "mini-stroke" (transient ischemic attack or TIA).

If patients are 75 or older, or if they weigh less than 132 pounds, or if they are taking anticoagulants (e.g., warfarin) or taking NSAIDs (e.g., ibuprofen or naproxen) for a long time, they should talk to their doctor, as they may be at an increased risk of bleeding.

If patients plan to have surgery or a dental procedure, they should tell their doctors that they are taking Effient.

Patients should not stop taking Effient without first talking to the doctor who prescribed it for them, as this may result in increased risk of a clot in their stent, a heart attack or death.

Patients should get medical attention right away if they develop any of the following unexpected symptoms: fever, weakness, yellowing of the skin or eyes, or if skin becomes very pale or dotted with purple spots. These symptoms may be signs of a rare but potentially life-threatening condition called TTP, which has been reported with other medicines in this class that are like Effient, sometimes after a short time (less than 2 weeks).

For more information about Effient, please see the Full Prescribing Information, including Boxed Warning (http://pi.lilly.com/us/effient.pdf), and Medication Guide (http://pi.lilly.com/us/effient-ppi.pdf). You may also learn more about Effient at www.Effient.com.

About Daiichi Sankyo

A global pharmaceutical innovator, Daiichi Sankyo Co., Ltd., was established in 2005 through the merger of two leading Japanese pharmaceutical companies. This integration created a more robust organization that allows for continuous development of novel drugs that enrich the quality of life for patients around the world. Areas of primary focus for Daiichi Sankyo research and development are thrombotic disorders, malignant neoplasm, diabetes mellitus, and autoimmune disorders. Equally important to the company are hypertension, hyperlipidemia or atherosclerosis and bacterial infections. For more information, visit www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is the U.S. subsidiary of Daiichi Sankyo Co., Ltd. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

This press release contains certain forward-looking statements about Effient for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndromes who are managed with percutaneous coronary intervention and reflects Daiichi Sankyo's and Lilly's current beliefs. However, as with any pharmaceutical product, there are

substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to date or that the product will be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filing with the United States Securities and Exchange Commission and Daiichi Sankyo's filings with the Tokyo Stock Exchange. Daiichi Sankyo and Lilly undertake no duty to update forward-looking statements.

Effient(R) is a registered trademark of Eli Lilly and Company.

Plavix(R) is a registered trademark of Sanofi-Aventis Corp.

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2. American Heart Association. Heart Disease and Stroke Statistics - 2008 Update. Dallas, TX. American Heart Association. (Pg. 14).

3. American Heart Association Heart Disease and Stroke Statistics - 2009 Updated. Dallas, TX. American Heart Association. (Pg. 2)

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