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## **Daiichi Sankyo and Lilly Announce TRILOGY ACS Results Regarding Effient® (Prasugrel) in Acute Coronary Syndrome UA/NSTEMI Patients to be Managed Medically without an Artery-Opening Procedure**

### **Study did not meet primary objective of demonstrating prasugrel superiority over clopidogrel in this patient population**

INDIANAPOLIS and TOKYO, Aug. 26, 2012 /PRNewswire/ -- Daiichi Sankyo Company, Limited (TSE: 4568) and Eli Lilly and Company (NYSE: LLY) today announced data from the TRILOGY ACS study, a phase III trial comparing prasugrel plus aspirin to clopidogrel plus aspirin in patients with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI), who were managed medically without an artery-opening procedure. At 30 months, 13.9 percent of prasugrel patients vs. 16.0 percent of clopidogrel patients experienced the combined primary endpoint of heart attack, stroke or cardiovascular (CV) death in patients under 75 years of age, the primary analysis population (HR=0.91; 95% CI: 0.79-1.05).(1) This outcome was not statistically significant (P=0.21). Different from other large-scale trials, TRILOGY ACS (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes) prospectively studied only the UA/NSTEMI population medically managed without revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery). (2) Results of this study were published in the *New England Journal of Medicine* and also presented during a late-breaking session at the ESC Congress 2012 (European Society of Cardiology) in Munich, Germany.

From a safety perspective, TRILOGY ACS showed that rates of TIMI major bleeding events (including life-threatening or fatal bleeds) did not differ significantly between the prasugrel plus aspirin and clopidogrel plus aspirin treatment groups in patients less than 75 years of age or in the overall study population.(1) In patients under age 75, non-CABG TIMI major bleeding occurred in 2.1 percent of prasugrel patients versus 1.5 percent of clopidogrel patients (HR=1.31, 95% CI: 0.81-2.11, P=0.27). (1) However, the rates of TIMI major or minor bleeding were higher in patients treated with prasugrel (3.3 percent of prasugrel patients versus 2.1 percent of clopidogrel patients; HR=1.54; 95% CI: 1.06-2.23; P=0.02).(1)

"TRILOGY ACS was designed to evaluate dual oral antiplatelet therapy in UA/NSTEMI patients who are managed medically without revascularization," said E. Magnus Ohman, M.D., Duke Clinical Research Institute and Chairperson of the TRILOGY ACS trial. "While the study did not demonstrate prasugrel was superior to clopidogrel in these patients, TRILOGY ACS provided some additional observations in this previously understudied population. The delayed treatment effect beyond 12 months observed in TRILOGY ACS had not been seen in earlier studies of shorter duration."

An analysis performed to account for multiple recurrent ischemic events suggested a lower risk among participants < 75 years treated with prasugrel (HR=0.85; 95% CI: 0.72—1.00; P=0.044).(1)

A post-hoc exploratory analysis observed a trend for a lower risk in heart attack, stroke and death among patients treated with prasugrel beyond one year; HRs and 95% CIs for the time period of < 12 months versus the time period of > 12 months comparing prasugrel versus clopidogrel for the primary efficacy endpoint were 0.99 (0.84-1.16) versus 0.72 (0.54-0.97) (interaction P=0.07).(1)

"Large-scale clinical trials in understudied populations, such as TRILOGY ACS, are important regardless of the result because they generate a sizeable amount of information for the medical community," said J. Anthony Ware, M.D., Group Vice President and Cardiovascular/Acute Care Platform Leader, Eli Lilly and Company. "We look forward to presenting additional data from the platelet function sub-study, analyses of the elderly population data, as well as genomics information in future peer-reviewed forums."

"While this is not the outcome we anticipated, we believe this study contributes to the knowledge base about ACS patients who are medically managed," said Glenn Gormley, M.D., Ph.D., Global Head of Research & Development and Senior Executive Officer, Daiichi Sankyo Company, Limited. "The group of patients in the TRILOGY ACS trial is different from those who participated in the prior TRITON-TIMI 38 trial, where almost all ACS patients underwent percutaneous intervention."

The TRILOGY ACS study was conducted by Daiichi Sankyo and Eli Lilly and Company in conjunction with the Duke Clinical Research Institute, one of the world's leading academic clinical research organizations and a part of Duke University Medical Center in Durham, North Carolina, United States.

Approved by the U.S. Food and Drug Administration in July 2009, Effient® (prasugrel) is indicated to reduce the rate of thrombotic CV events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with an artery-opening procedure called PCI as follows: [1] patients with unstable angina (UA) or non—ST-elevation myocardial infarction (NSTEMI); [2] patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI. The loading dose (LD) of Effient is 60 mg and the maintenance dose (MD) is 10 mg once daily. Effient is available in 5-mg and 10-mg tablets.[iii] The Effient indication is based on the results of the TRITON-TIMI 38 trial.

### **About TRILOGY ACS**

TRILOGY ACS (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes) began in June 2008 and reached a total enrollment of 9,326 patients at more than 900 hospitals in 52 countries worldwide.(2)

TRILOGY ACS was a multi-center, double-blind, randomized, controlled trial to evaluate the safety and efficacy of prasugrel plus aspirin compared to clopidogrel plus aspirin in UA/NSTEMI patients who were to be medically managed without revascularization. The primary endpoint was the time to occurrence of the first instance of the composite endpoint of CV death, heart attack or stroke. The sample size in the trial was selected to detect a 22 percent relative risk reduction in patients treated for up to 30 months with prasugrel compared with clopidogrel.(2)

Inclusion criteria for the study included at least one of the following high-risk features in UA/NSTEMI patients: age greater than 60 years, prior myocardial infarction, diabetes mellitus and/or prior revascularization (PCI or CABG).(2) Exclusion criteria included planned PCI or CABG, STEMI as the initial event, and medical management decision more than 72 hours after onset of event without clopidogrel treatment.(2)

Prasugrel loading and maintenance dosages in TRILOGY ACS were adjusted for the medically managed patient population enrolled and differ from the current indicated dosages for ACS-PCI patients.(2) Patients under the age of 75 and weighing more than 60 kg received a 10 mg MD of prasugrel. Prasugrel dosage adjustments (5 mg) were made for very elderly patients (75 years of age and older) and for those < 60 kg; patients with prior TIA/stroke were excluded.(2)

The current prasugrel indication in ACS patients intended for planned PCI, is a single 60 mg LD followed by a once-daily 10 mg MD.(3) A single 60 mg LD of prasugrel followed by a MD of prasugrel at a 5 mg once daily dose, co-administered with aspirin, can be considered for lower weight patients (< 60 kg) with ACS-PCI.(3)

Safety endpoints evaluated included bleeding as measured by GUSTO and TIMI criteria; plus systematic collection of neoplasm data (all suspected events to be adjudicated by an Oncology Clinical End Point Committee).(2)

More than 90 percent of the patients in the study were treated with clopidogrel prior to randomization, per the guidelines for secondary prevention.(1) Although all patients in the study were committed to be treated medically without revascularization for the index event, a small percentage of patients less than 75 years of age underwent revascularization (7.9 percent) after randomization.(1)

More information on the TRILOGY ACS trial and its design is available at: <http://clinicaltrials.gov/ct2/show/NCT00699998>.

### **About Acute Coronary Syndrome**

ACS, which includes heart attack and a type of chest pain called unstable angina (UA), affects more than one million people in the United States annually.(4) The annual incidence of new heart attacks is estimated to be approximately 610,000 and about 325,000 people will have a recurrent attack. There are two main types of heart attack: non-ST-segment elevation, or NSTEMI, and ST-segment elevation, or STEMI. STEMI heart attacks are often considered more severe as the artery is often fully blocked, preventing blood flow to the heart.

Each year, approximately 596,000 people undergo PCI, which typically includes the implantation of a stent that restores blood flow to blocked arteries in the heart. The number of UA or NSTEMI ACS patients worldwide who are managed without acute coronary interventions, such as PCI, has ranged from 32 percent to almost 60 percent over the last few years.(5,6) In many cases, these ACS patients may have complex coronary anatomy, comorbidities or other high-risk factors that prevent surgical intervention.

ACS results in significant illness and death, costing Americans more than \$150 billion each year.(7) Nearly 60 percent of the U.S healthcare costs of ACS are due to re-hospitalization. Strategies to prevent recurrent heart attacks and re-hospitalization are important to improve patient outcomes and reduce the cost burden of ACS.

### **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 indicated to reduce the rate of

thrombotic CV events (including stent thrombosis) in patients with ACS who are to be managed with an artery-opening procedure called PCI as follows: [1] patients with UA or NSTEMI; [2] patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI. The loading dose of Effient is 60 mg and the maintenance dose is 10 mg once daily. Effient is available in 5-mg and 10-mg tablets.

## **Important Safety Information**

### ***What is the most important information patients should know about Effient?***

Effient® (prasugrel) can cause 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 fatal. Patients should not take Effient if they currently have abnormal bleeding, such as stomach or intestinal bleeding, bleeding in their head, or have a history of stroke, or "mini-stroke" (also known as transient ischemic attack or TIA), or are allergic to prasugrel or any of the ingredients in Effient.

Patients should get medical help right away if they suddenly have slurring of speech, weakness or numbness in one part of their body, blurry vision, and/or severe headache. These may be symptoms of a stroke or TIA. If patients have a stroke or TIA while taking Effient, their doctor will probably stop Effient. Before having any surgery, patients should talk to their doctor about stopping Effient. If possible, patients should stop taking Effient at least 1 week (7 days) before any surgery, as instructed by their doctor who prescribed Effient.

Patients may also have a higher risk of bleeding if they take Effient and they: a) are age 75 or older, b) weigh less than 132 pounds, c) are taking anticoagulants (eg, warfarin) or regular daily use of NSAIDs, d) have had recent trauma, such as an accident or surgery, e) have severe liver problems, or f) have a stomach ulcer.

Patients should not stop taking Effient without talking to the doctor who prescribes it for them. People who are treated with angioplasty and have a stent, and stop taking Effient too soon, have a higher risk of a blood clot in the stent, having a heart attack, or dying.

### ***What should patients tell their doctor before taking Effient?***

Patients should tell their doctor about all of their medical conditions, allergies, and medicines they are taking.

### ***What are the possible side effects of Effient?***

Bleeding is the most common side effect of Effient.

TTP, a rare but life-threatening condition, has been reported with Effient, sometimes after a short time (less than 2 weeks). Patients should get medical attention right away if they develop the following unexpected symptoms of TTP: fever, weakness, yellowing of the skin or eyes, or if skin becomes very pale or dotted with purple spots.

Serious allergic reactions can happen with Effient, or if the patient has had a serious allergic reaction to the medicines Plavix® (clopidogrel) or ticlopidine. Patients should get medical help right away if they get any of these symptoms of a severe allergic reaction: swelling or hives of their face, lips, in or around their mouth, or throat, trouble breathing or swallowing, chest pain or pressure, dizziness or fainting.

Other side effects may occur.

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

## **About Daiichi Sankyo**

The Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, hyperlipidemia, and bacterial infections, the Group is engaged in the development of treatments for thrombotic disorders and focused on the discovery of novel oncology and cardiovascular-metabolic therapies. Furthermore, the Daiichi Sankyo Group has created a "Hybrid Business Model," which will respond to market and customer diversity and optimize growth opportunities across the value chain. For more information, please visit [www.daiichisankyo.com](http://www.daiichisankyo.com). Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit [www.dsi.com](http://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](http://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<sup>®</sup> is a registered trademark of Eli Lilly and Company.

Plavix<sup>®</sup> is a registered trademark of Sanofi-Aventis Corp.

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