PEGASUS-TIMI 54 Study Shows That Long-Term Treatment with BRILINTA Reduced Thrombotic Cardiovascular Events in Patients with a History of Heart Attack

Data from 21,000 patient study presented at American College of Cardiology 64th Annual Scientific Session and simultaneously published in New England Journal of Medicine

March 14, 2015 - WILMINGTON, Del.

(Business Wire) AstraZeneca (NYSE:AZN) today announced full results from the PEGASUS-TIMI 54 study, a large-scale outcomes trial that investigated BRILINTA® (ticagrelor) tablets plus low dose aspirin, compared to placebo plus low dose aspirin, for chronic secondary prevention of atherothrombotic events in patients who had experienced a heart attack one to three years prior to study enrollment.

Key findings:

- Both 90mg and 60mg study doses of ticagrelor with aspirin significantly reduced the primary composite endpoint of cardiovascular (CV) death, myocardial infarction (MI) or stroke compared to placebo.
- As expected with an oral antiplatelet, TIMI Major Bleeding[1], the study's primary safety endpoint, was higher with both doses of ticagrelor plus aspirin compared to placebo plus aspirin. Importantly, the rates of intracranial hemorrhage (bleeding within the skull) and fatal bleeding were low and similar between study groups and the placebo arm.

The data were presented during the opening late-breaking clinical trial session of the American College of Cardiology's 64th Annual Scientific Session and Expo, and also simultaneously published in the *New England Journal of Medicine* online.

Elisabeth Björk, Vice President, Head of Cardiovascular and Metabolic Diseases, Global Medicines Development, AstraZeneca, said: "As a company we are committed to furthering cardiovascular research and are proud to have delivered the PEGASUS-TIMI 54 study, AstraZeneca's largest clinical trial, involving more than 21,000 patients worldwide. Building on the landmark PLATO trial in acute coronary syndrome, the positive PEGASUS study adds to the body of evidence for BRILINTA and is the first prospective trial to evaluate longer term dual antiplatelet therapy in higher risk patients with a history of a heart attack.

"We have just submitted regulatory filings to the European Medicines Agency and the US

Food and Drug Administration and we look forward to working with these agencies towards a potential new indication in major markets."

Recent research has shown that one in five patients will have a further heart attack, stroke or CV death in the subsequent three years following a heart attack, even if patients were event free after 12 months. For patients more than one year from a heart attack, the current standard of care is aspirin alone. The PEGASUS-TIMI 54 study was designed to investigate the effect of adding ticagrelor 60mg or 90mg twice daily to low dose aspirin on reducing the risk of CV death, heart attack or stroke in patients aged 50 and older with a history of heart attack and one additional CV risk factor.

Ticagrelor is not approved for secondary prevention of atherothrombotic events in patients with a history of heart attack beyond one year.

Efficacy Findings

In this trial, both study doses of ticagrelor significantly reduced the primary endpoint of CV death, MI or stroke compared to placebo. The rates at 3 years were 7.85% in the ticagrelor 90mg arm, 7.77% in the ticagrelor 60mg arm, and 9.04% in the placebo arm (Hazard Ratio (HR) for ticagrelor 90mg vs placebo 0.85, 95% CI 0.75 – 0.96, P=0.0080; HR for ticagrelor 60mg vs placebo 0.84, 95% CI 0.74 – 0.95, P=0.0043).

The effect of ticagrelor on each of the components of the primary endpoint was consistent. A numerical decrease in the secondary endpoints of cardiovascular death and all cause mortality was observed, but did not reach statistical significance.

In addition, the primary efficacy endpoint of both doses of ticagrelor appeared consistent across major subgroups including age, sex, index MI type (STEMI/NSTEMI), time from qualifying MI, diabetes, aspirin dose, history of percutaneous intervention (angioplasty), and geographical region.

Safety Findings

As expected, TIMI Major bleeding was higher with both doses of ticagrelor compared to placebo, with rates at 3 years of 2.60% in the ticagrelor 90mg arm, 2.30% in the ticagrelor 60mg arm, and 1.06% in the placebo arm (HR for ticagrelor 90mg vs placebo 2.69, 95% CI 1.96 – 3.70, p<0.001; HR for ticagrelor 60mg vs placebo 2.32, 95% CI 1.68 – 3.21, p<0.001).

However, the rates of fatal bleeding or intracranial hemorrhage were low and similar between treatment arms.

Fatal bleeding rates at 3 years were 0.11% in the ticagrelor 90mg arm, 0.25% in the ticagrelor 60mg arm, and 0.26% in the placebo arm (HR for ticagrelor 90mg vs placebo 0.58, 95% CI 0.22 – 1.54, p=0.27; HR for ticagrelor 60mg vs placebo 1.00, 95% CI 0.44 – 2.27, p=1.00).

Intracranial hemorrhage rates at 3 years were 0.56% in the ticagrelor 90mg arm, 0.61% in the ticagrelor 60mg arm, and 0.47% in the placebo arm (HR for ticagrelor 90mg vs placebo 1.44, 95% CI 0.83 – 2.49, p=0.19; HR for ticagrelor 60mg vs placebo 1.33, 95% CI 0.77 – 2.31, p=0.31).

The PEGASUS-TIMI 54 study, AstraZeneca's largest outcomes trials involving more than 21,000 patients from over 1,100 sites in 31 countries, is part of the PARTHENON program. The PLATO study, involving over 18,000 patients, was the first study in the program and is the basis on which ticagrelor has been approved in over 100 countries and included in 12 major ACS treatment guidelines globally. Further ongoing PARTHENON studies are assessing ticagrelor for the prevention of cardiovascular events in patients with peripheral arterial disease, ischaemic stroke or transient ischaemic attack, and in patients with diabetes and coronary atherosclerosis.

BRILINTA is not approved for secondary prevention of atherothrombotic events in patients with a history of heart attack beyond one year or for the prevention of cardiovascular events in patients with peripheral arterial disease, stroke, diabetes or atherosclerosis.

BRILINTA is indicated to reduce the rate of thrombotic cardiovascular (CV) events in patients with ACS (unstable angina [UA], non–ST-elevation myocardial infarction [NSTEMI], or ST-elevation myocardial infarction [STEMI]). BRILINTA has been shown to reduce the rate of a combined end point of CV death, myocardial infarction (MI), or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with percutaneous coronary intervention (PCI), it also reduces the rate of stent thrombosis.

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin > 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin > 100 mg daily.

IMPORTANT SAFETY INFORMATION ABOUT BRILINTA (ticagrelor) 90-MG TABLETS

WARNING: (A) BLEEDING RISK, (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

A. BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal,**

bleeding

- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events**

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75 mg - 100 mg per day**

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage and active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure; it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins. BRILINTA is also contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product

WARNINGS AND PRECAUTIONS

- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor
- Premature discontinuation increases the risk of MI, stent thrombosis, and death
- Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes
- BRILINTA is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors and potent CYP3A inducers. Avoid simvastatin and lovastatin doses >40 mg
- Monitor digoxin levels with initiation of, or any change in, BRILINTA therapy

ADVERSE REACTIONS

- The most commonly observed adverse reactions associated with the use of BRILINTA vs clopidogrel were Total Major Bleeding (11.6% vs 11.2%) and dyspnea (14% vs 8%)
- In clinical studies, BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment

Please read full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/safety/medwatch or call 1-800-FDA-1088.

– ENDS –

NOTES TO EDITORS

[1] TIMI Major Bleeding Classification:

- Any intracranial bleeding, or
- Clinically overt signs of haemorrhage associated with a drop in hemoglobin (Hgb) of ?5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of ?15%), or
- Fatal bleeding (a bleeding event that directly led to death within 7 days).

About PEGASUS-TIMI 54

PEGASUS-TIMI 54 (PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome – Thrombolysis In Myocardial Infarction Study Group) is AstraZeneca's largest ever outcomes trials with more than 21,000 patients from over 1,100 sites in 31 countries in Europe, the Americas, Africa and Australia/Asia. It was conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group from Brigham and Women's Hospital (Boston, MA, USA).

About BRILINTA®

BRILINTA is a direct-acting, selective and reversibly binding P2Y12 receptor antagonist in a chemical class called cyclo-pentyl-triazolo-pyrimidines (CPTPs). BRILINTA works by inhibiting platelet activation.

BRILINTA (90mg) is indicated to reduce the rate of thrombotic CV events in patients with ACS (unstable angina [UA], non–ST-elevation myocardial infarction [NSTEMI], or ST-elevation myocardial infarction [STEMI]). BRILINTA has been shown to reduce the rate of a combined

end point of CV death, MI, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with percutaneous coronary intervention, it also reduces the rate of stent thrombosis.

BRILINTA is a registered trademark of the AstraZeneca group.

About the Thrombolysis in Myocardial Infarction (TIMI) Study Group

The TIMI Study Group is affiliated with Brigham and Women's Hospital and Harvard Medical School and is located in Boston, Massachusetts. It is one of the oldest cardiovascular academic research organization in the United States and has conducted numerous practice-changing clinical trials in patients with CV disease or risk factors for CV disease.

About AstraZeneca

AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialization of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information please visit: www.astrazeneca.com.

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