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Investor News

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Data from COMPASS study, including 27,395 patients, presented at ESC Congress 2017:

Bayer's Xarelto® significantly lowered the combined risk of stroke, cardiovascular death and heart attack in patients with chronic coronary or peripheral artery disease by 24%

- Importantly, rivaroxaban vascular dose, 2.5 mg twice daily, plus aspirin 100 mg once daily showed an unprecedented 42% relative risk reduction in stroke and 22% in cardiovascular death compared with aspirin 100 mg once daily alone
- Bleeding rates were low, and while major bleeding was increased, notably there was no significant increase in intracranial or fatal bleeding
- This combination regimen demonstrated a substantial improvement in net clinical benefit of 20%

Leverkusen, Germany, August 27, 2017 – In the Phase III COMPASS study, Bayer's Factor Xa inhibitor, rivaroxaban (Xarelto®) vascular dose, 2.5 mg twice daily, plus aspirin 100 mg once daily reduced the risk of the composite outcome of stroke, cardiovascular (CV) death and heart attack by 24% (relative risk reduction) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD). The study compared this combined approach with aspirin 100 mg once daily alone. Patients included in the study had already received guideline recommended therapy for hypertension, high cholesterol and diabetes. A 5 mg twice daily dose of rivaroxaban was also investigated but the difference in the primary outcome did not reach statistical significance. Data were revealed during two Hot Line presentations at ESC Congress 2017 in Barcelona, Spain, 26–30 August. The COMPASS findings were simultaneously published in *The New England Journal of Medicine*.

The benefit shown in the combined efficacy endpoint, major adverse cardiovascular events (MACE), for rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily was mainly driven by a significant reduction of stroke (42%) and CV death (22%). The regimen also reduced the risk of heart attack by 14% however this result was not

statistically significant. This combination regimen demonstrated a substantial 20% improvement in net clinical benefit, defined as the reduction in stroke, CV death, and heart attack balanced against the most serious bleeding events. The hazard ratio for all-cause mortality was 0.82 (95% CI 0.71-0.96; P=0.01). Bleeding incidence rates were low, and while there was an increase in major bleeding, notably there was no significant increase in fatal or intracranial bleeding. Importantly, in the PAD patient population, the combination of major adverse limb events plus all major amputations of a vascular cause were reduced significantly.

Cardiovascular disease, which includes CAD and PAD, is responsible for approximately 17.7 million deaths every year, representing 31% of all global deaths. Additionally, patients with cardiovascular disease have a reduction in life expectancy of over 7 years. CAD and PAD are caused by atherosclerosis, a chronic, progressive disease which is characterised by a build-up of plaque in the arteries. Patients with these conditions are at risk of thrombotic events which may lead to disability, loss of limb and loss of life.

“CAD and PAD remain a major public health burden. Despite the routine use of guideline-recommended antiplatelet therapy, event rates remain substantial,” said John Eikelboom, Associate Professor, Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Canada. “These findings for the vascular dose of rivaroxaban are arguably the most significant in antithrombotic therapy in this disease area to date. Once approved, this vascular dose provides us with a major opportunity to change clinical practice and better treat patients.”

“Bayer has a long and successful heritage in cardiology and our medicines have already improved the lives of millions of patients across the world,” said Dr Joerg Moeller, Member of the Executive Committee of Bayer AG's Pharmaceutical Division and Head of Development. “The COMPASS study is the first of its kind; no other NOAC has been studied in this patient population and the magnitude of these results clearly shows the benefit rivaroxaban could bring to patients with CAD or PAD. We will now work with regulatory authorities to make this treatment option available to patients as soon as possible.”

The COMPASS study is the largest clinical study of rivaroxaban to date. The study was stopped approximately one year ahead of schedule due to overwhelming efficacy and Bayer, Janssen and the Population Health Research Institute (PHRI) are working towards offering rivaroxaban to study participants in an open-label extension trial. Rivaroxaban is

the only non-vitamin K antagonist oral anticoagulant (NOAC) investigated in secondary prevention for cardiovascular disease in stable / chronic CAD or PAD patients.

COMPASS is part of the extensive evaluation of rivaroxaban which, by the time of completion, will include more than 275,000 patients in clinical trials and real-world studies. In addition to COMPASS, Bayer is investigating rivaroxaban in other studies in the cardiovascular field including VOYAGER PAD and COMMANDER-HF.

About COMPASS

The Phase III randomised controlled COMPASS study is the largest clinical study of rivaroxaban to date with 27,395 patients. COMPASS was conducted in collaboration with the PHRI in more than 600 research sites across more than 30 countries worldwide.

The COMPASS study evaluated the use of rivaroxaban for the prevention of major adverse cardiac events (MACE) including CV death, myocardial infarction (MI) and stroke in patients with coronary artery disease, peripheral artery disease or both.

Patients received a run-in of aspirin 100 mg once daily for 30 days, and were then randomised in a 1:1:1 ratio to receive (with or without pantoprazole):

- Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily
- Rivaroxaban 5 mg twice daily
- Aspirin 100 mg once daily

Patients who were being treated with a proton pump inhibitor (PPI) prior to enrolment continued with their existing medication. Patients without a continued need for PPI treatment were randomised to pantoprazole or its placebo.

Efficacy Outcomes

For the primary efficacy outcome, rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily was superior to aspirin 100 mg once daily alone for the prevention of the composite endpoint of stroke, CV death and MI (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.66-0.86; P<0.001). Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily reduced the risk of stroke by 42% (HR 0.58; 95% CI 0.44-0.76; P<0.001), CV death by 22% (HR 0.78; 95% CI 0.64-0.96; P=0.02) and heart attack by 14% (HR 0.86;

95% CI 0.70-1.05; P=0.14). Rivaroxaban 5 mg twice daily also reduced the composite outcome of stroke, CV death and MI but these results were not statistically significant.

Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily compared with aspirin 100 mg once daily alone improved the net clinical benefit defined as the composite of stroke, CV death, MI, fatal bleeding or symptomatic bleeding in a critical organ (HR 0.80; 95% CI 0.70-0.91; P<0.001). Rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily did not improve the net clinical benefit.

Safety Outcomes

The main safety outcome was a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding, and included fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalisation (including presentation to an acute care facility without overnight stay). Unlike the ISTH criteria, all bleeding leading to presentation to an acute care facility or hospitalisation was considered as major.

Rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily compared with aspirin 100 mg once daily alone increased the risk of major bleeding (HR 1.70, 95% CI 1.40-2.05, P<0.001). Most of the major bleeding was into the gastrointestinal tract, with no significant increase in fatal bleeds, intracranial bleeds or symptomatic bleeds into a critical organ.

Although there was also a significant increase in major bleeding as defined using the non-modified ISTH scale, incidence rates using this definition were approximately one-third lower when compared to those obtained when using the modified ISTH criteria.

About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) and is marketed under the brand name Xarelto®. Xarelto is approved for seven indications, protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other NOAC:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors

- The treatment of pulmonary embolism (PE) in adults
- The treatment of deep vein thrombosis (DVT) in adults
- The prevention of recurrent PE and DVT in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of VTE in adult patients undergoing elective knee replacement surgery
- The prevention of atherothrombotic events (cardiovascular death, myocardial infarction or stroke) after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers and no prior stroke or transient ischaemic attack (TIA) when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine

Whilst licences may differ from country to country, across all indications Xarelto is approved in more than 130 countries.

Rivaroxaban was discovered by Bayer, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer and in the U.S. by Janssen Pharmaceuticals, Inc. (Janssen Research & Development, LLC and Janssen Pharmaceuticals, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life-threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a very high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a Xarelto Patient Card for patients to support best practice.

To learn more about thrombosis, please visit www.thrombosisadviser.com

To learn more about Xarelto, please visit www.xarelto.com

Bayer: Science For A Better Life

Bayer is a global enterprise with core competencies in the Life Science fields of health care and agriculture. Its products and services are designed to benefit people and improve their quality of life. At the same time, the Group aims to create value through innovation, growth and high earning power. Bayer is committed to the principles of sustainable development and to its social and ethical responsibilities as a corporate citizen. In fiscal 2016, the Group employed around 115,200 people and had sales of EUR 46.8 billion. Capital expenditures amounted to EUR 2.6 billion, R&D expenses to EUR 4.7 billion. These figures include those for the high-tech polymers business, which was floated on the stock market as an independent company named Covestro on October 6, 2015. For more information, go to www.bayer.com.

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