News Release

Two large Xarelto™ studies support effectiveness of dual pathway inhibition in patients with coronary artery disease and/or peripheral artery disease

- Results from the extension part of the COMPASS study support the long-term use of Xarelto (rivaroxaban) plus aspirin for vascular protection in patients with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD)
- The XATOA registry provides additional evidence of the benefit of a dual pathway inhibition (DPI) for patients with vascular disease at high risk of cardiovascular (CV) events in routine clinical practice
- The studies reinforce the findings of the COMPASS study and provide additional confidence in DPI treatment in patients with CAD and/or PAD

Berlin, May 23, 2022 – Two studies with Bayer´s Factor Xa inhibitor rivaroxaban (Xarelto), the Long-Term Open Label Extension (LTOLE) of the COMPASS trial and the XATOA registry, provide complementary evidence of the benefits of dual pathway inhibition (DPI), defined as the combination of the vascular dose of Xarelto (2.5 mg twice daily) and aspirin. The Phase III COMPASS study, published in 2017 in the New England Journal of Medicine and the largest clinical study of Xarelto to date with 27,395 patients, confirmed that Xarelto 2.5 mg twice daily plus aspirin 100 mg once daily reduced the risk of the composite outcome of stroke, cardiovascular death and heart attack by 24% (relative risk reduction) in patients with chronic coronary artery disease and/or peripheral artery disease. The findings of the LTOLE study and the XATOA registry were published in European Heart Journal - Cardiovascular Pharmacotherapy, one of the official journals of the European Society of Cardiology (ESC).

The LTOLE part of the COMPASS study found that continued treatment with Xarelto 2.5 mg twice daily and aspirin 100 mg once daily for up to 3 years was associated with incidence rates for major adverse cardiovascular events (cardiovascular death, stroke, or
myocardial infarction) and for bleeding that were similar to or lower than those seen during the randomized treatment phase.

“The benefits of using a combination therapy in patients with chronic CAD and/or PAD at high risk for CV events have been clearly shown in the COMPASS trial,” said Professor John Eikelboom, McMaster University in Hamilton, Canada and lead author of the COMPASS and LTOLE studies. “Now the findings in the long-term open label extension part further highlight and support long-term use of rivaroxaban plus aspirin for vascular protection in patients at high risk of CV events. This regimen adds an important treatment option to clinical practice.”

DPI, the combination of the vascular dose of Xarelto (2.5 mg twice daily) and aspirin (75 – 100 mg once daily), is widely approved by healthcare authorities for use in patients with CAD, PAD, or both having increased vascular risk. However outside the context of a randomized trial, clinical characteristics of patients at risk, bleeding rates and clinical event rates in patients receiving DPI were not available. The XATOA study investigated these for the first time in registry, revealing that patients at high risk due to vascular disease are being prioritized for DPI therapy in clinical practice. Rates of major adverse cardiovascular events (MACE) were similar to these in the COMPASS study; rates of major adverse limb events (MALE) were higher, consistent with the greater proportion of patients with PAD in the study.

“The XATOA study was a first of its kind,” said Professor Keith Fox, University of Edinburgh, and lead author of the XATOA registry. “Patient outcomes overall were consistent with the COMPASS study. Major bleeding rates were even lower. The findings give us additional evidence of the benefits of using DPI in patients at increased risk of vascular events and should be considered as treatment option.”

**About the COMPASS and COMPASS LTOLE studies**

In the double-blind part of the Phase III COMPASS study the vascular dose of Xarelto, 2.5 mg twice daily, plus aspirin 100 mg once daily reduced the risk of stroke, myocardial infarction, or cardiovascular death and all-cause mortality in patients receiving a high standard of risk factor management for CAD and/or PAD. The treatment resulted in an 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.
Of the patients originally randomized in COMPASS, 12,964 were subsequently enrolled in the open-label extension part, from 455 sites in 32 countries. All patients received the vascular dose of Xarelto plus aspirin for a median of 374 days. They were followed every 6 months to evaluate adherence and safety, and to collect clinical outcomes, including stroke, MI, and mortality.

The COMPASS study was a collaboration between Bayer, Janssen Research & Development LLC and the Population Health Research Institute (PHRI), a joint institute of McMaster University and Hamilton Health Sciences.

**About the XATOA study**
XATOA was an international, multi-center, prospective, single-arm study designed to provide insights into the clinical characteristics of patients selected for DPI with CAD, PAD or both and their clinical outcomes and bleeding rates in clinical practice. 5,532 patients were included, and most were treated only with aspirin prior to enrollment.

Clinical outcomes of interest included major adverse cardiovascular events and major adverse limb events. The safety outcome was ISTH major bleeding. Outcome definitions were harmonized with those of the COMPASS study to allow comparisons of the data.

**About CAD and PAD**
Cardiovascular diseases (CVD), including coronary artery disease (CAD) and peripheral artery disease (PAD), account for around 1 in every 3 deaths worldwide. Despite advances in management, CVDs continue to place a significant burden on healthcare, social care, and financial systems.

CAD, or ischemic heart disease, is the foremost single cause of mortality globally. PAD is a common circulatory problem in which narrowing of the arteries reduces blood flow, mainly to the lower limbs, increasing the risk for major CV events. PAD is estimated to affect over 200 million people worldwide.

**About Rivaroxaban (Xarelto™)**
Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) worldwide and is marketed under the brand name Xarelto. Xarelto is approved for 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/or 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 after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine
• The prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk for ischemic events when co-administered with acetylsalicylic acid (ASA)
• Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment
• Thromboprophylaxis (prevention of VTE and VTE related events) in children aged two years and older with congenital heart disease who have undergone the Fontan procedure

Xarelto is approved in more than 130 countries, although the approved labelling, including the number of indications may differ from country to country. Since launch in 2008, more than 100 million patients have been treated.

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 therapies used to prevent or treat serious illnesses and potentially life-threatening conditions. Before initiating treatment 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 and www.vascularadviser.com

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

About Bayer
Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and the planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to driving sustainable development and generating a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2021, the Group employed around 100,000 people and had sales of 44.1 billion euros. R&D expenses before special items amounted to 5.3 billion euros. For more information, go to www.bayer.com.

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rib (2022-0048E)
Forward-Looking Statements
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