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News Release

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Study reaffirms safety and efficacy profile of Xarelto™ for the prevention of stroke in patients with atrial fibrillation

- First results from RELOADED, an observational study in the EU, indicate that non-vitamin-K oral anticoagulants (NOACs) like Xarelto provide a benefit in renal preservation over time when compared to the vitamin-K antagonist (VKA) phenprocoumon
 - The data from the comparative effectiveness study in Germany confirm an improved safety outcome and comparable effectiveness for Xarelto compared with phenprocoumon in patients with non-valvular atrial fibrillation (NVAf), including those with renal insufficiency¹
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Berlin, April 29, 2019 – The results of an observational study comparing Xarelto (rivaroxaban) to phenprocoumon¹, the most used vitamin-K antagonist (VKA) in Germany, have been presented at the 85th Annual Conference of the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie (DGK)). The study demonstrated that in patients with atrial fibrillation and chronic kidney disease Xarelto delivered comparable effectiveness and better safety outcomes when compared to phenprocoumon. Improved renal preservation surrogate outcomes also indicate that NOACs like Xarelto can preserve renal function over time. The relative risk of patients with chronic kidney disease progressing to end stage renal disease and therefore requiring dialysis was lowered by 73% compared to VKA.

The use of NOACs is generally recommended as the Standard of Care for the prevention of stroke in patients with atrial fibrillation (reference 2016 ESC Guidelines²). However there has been a lack of data from daily clinical practice available for NOACs vs. phenprocoumon – especially in patients with renal insufficiency.

The observational study of anonymized German healthcare claims data from January 1st, 2013 to June 30th, 2017, now compares outcomes in patients treated with different

NOACs or phenprocoumon and confirms beneficial findings of the effectiveness and safety of NOACs. In addition, NOACs seem to be associated with a beneficial effect of supporting preservation of renal function over time when compared to phenprocoumon.

Until now, there have been no data from clinical practice available regarding preservation of renal function in patients with chronic kidney disease. “For the first time ever, the RELOADED study has compared the effectiveness and safety outcomes of different NOACs, including Xarelto, to the VKA phenprocoumon in patients with atrial fibrillation and renal impairment,” said Professor Hendrik Bonnemeier, Department of Internal Medicine at the University Hospital Schleswig-Holstein, Kiel, Germany. “The findings suggest consistently positive results for Xarelto across a broad spectrum of patients in everyday life and in clinical studies. Xarelto is a valuable treatment option for the prevention of stroke in patients with atrial fibrillation, including those with comorbidities such as renal failure.”

The beneficial effect of Xarelto supporting preservation of renal function over time when compared to VKA was first seen in a post-hoc analysis of the phase 3 ROCKET AF trial. These results were confirmed by data from 2017, based on a retrospective analysis of a large U.S. administrative database. It found NOACs, including Xarelto, to be associated with a lower incidence of both chronic and acute renal events when compared to warfarin³. Vascular calcification affecting the kidneys is a possible side effect of VKA treatment and the results now confirm a further advantage for NOACs in this regard. This has been also reflected in the latest US guidelines (AHA/ACC/HRS) for Xarelto and dabigatran.

In the last 20 years, atrial fibrillation has become one of the most significant public health problems and is a major driver of increasing national healthcare costs⁴. Atrial fibrillation is frequently associated with cardiac disease and comorbidities such as renal failure and there is a strong relationship between renal function and thromboembolic events in patients with non-valvular atrial fibrillation.

About the RELOADED study

A total of 22,339 patients started treatment with Xarelto, of which 5,121 patients had renal disease, and a total of 23,552 patients started treatment with phenprocoumon, of which 7,289 had renal disease. Important exclusion criteria for the study included valvular

conditions in the baseline period, cardiac valve surgery in the 365 days prior to the index date, venous thromboembolism (VTE) in the previous or same quarter of the index date, hip or knee replacement surgery in the 60 days prior to the index date, pregnancy, as well as end-stage kidney disease (ESRD) or a claim for dialysis in the baseline period.

On average, patients were followed-up over a period of 1.1 years. In the overall population, treatment with Xarelto decreased the risk of intracranial hemorrhage (ICH) by nearly half when compared to phenprocoumon treatment (hazard ratio (HR) 0.57 (0.43; 0.75). Beneficial effects were also observed for Xarelto vs phenprocoumon when analyzing risks for fatal bleedings with a HR of 0.78 (0.6; 1.03) in the overall population and a HR of 0.63 (0.42; 0.95) in the renal impairment population.

For the endpoint ESRD/dialysis, a strong beneficial effect was seen for NOACs over phenprocoumon. In comparison to phenprocoumon, Xarelto lowered the risk for ESRD/dialysis by nearly two-thirds in the overall population (HR 0.34 (0.23; 0.51)) and by nearly three-quarters in the renal impairment population (HR 0.27 (0.16; 0.43)). For the endpoint acute kidney injury, Xarelto also showed a benefit compared to phenprocoumon: HR 0.81 (0.66; 1.00) in the overall population and 0.77 (0.58; 1.01) in the renal impairment population. This benefit on acute kidney injury was not observed in the other NOACs analyzed.⁵

About Xarelto™

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 eight 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 (CV) death, myocardial infarction (MI) 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
- The prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk for ischaemic events when co-administered with acetylsalicylic acid

Xarelto is approved in more than 130 countries, whilst the approved labeling, including the number of indications may differ from country to country.

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 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

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 benefit people by supporting efforts to overcome the major challenges presented by a growing and aging global population. At the same time, the Group aims to increase its earning power and create value through innovation and growth. Bayer is committed to the principles of sustainable development, and the Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2018, the Group employed around 117,000 people and had sales of 39.6 billion euros. Capital expenditures amounted to 2.6 billion euros, R&D expenses to 5.2 billion euros. For more information, go to www.bayer.com.

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rib (2019-0121)

Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

¹ Abstract RELOADED for DGK, 26.04.2019.

² Kirchhof P et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7;37(38):2893-2962.

³ Yao X, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. JACC 2017 Nov 28;70; 2621-32.

⁴ Zoni-Berisso M, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014 Jun 16;6:213-20.

⁵ Xarelto should be used with caution in patients with severe renal impairment (creatinine clearance 15-29 ml / min). Use in patients with creatinine clearance <15 ml / min is not recommended (see prescribing information).