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## Investor News

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### **Bayer's Xarelto in Combination with Single Antiplatelet Therapy Receives Positive CHMP Opinion for Treatment of Patients with Atrial Fibrillation requiring oral Anticoagulation and undergoing Percutaneous Coronary Intervention with Stent Placement**

- Positive CHMP Opinion is based on data from the Phase IIIb PIONEER AF-PCI study, which demonstrated significantly reduced rates of clinically significant bleeding with Xarelto compared with VKA in patients with non-valvular atrial fibrillation (AF) who require oral anticoagulation and are also receiving antiplatelet therapy after percutaneous coronary intervention (PCI) with stent placement<sup>1</sup>
  - PIONEER AF-PCI is the first and currently only randomised clinical trial of a non-vitamin K antagonist oral anticoagulant (NOAC) in this patient population
  - Final decision of European Commission expected by the end of this year
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**Leverkusen, Germany, July 21, 2017** – Bayer AG announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion on a label update regarding the use of 15 mg once daily of the oral Factor Xa inhibitor Xarelto<sup>®</sup> (Rivaroxaban) in combination with a P2Y12 inhibitor for the treatment of patients with non-valvular atrial fibrillation (AF) who require oral anticoagulation and undergo percutaneous coronary intervention (PCI) with stent placement. The final decision of the European Commission is expected by the end of this year.

“The recommendation by the CHMP is an important step towards improved management of these patients, who are at high risk of thrombosis and need anticoagulation therapy because they have atrial fibrillation and received a stent placement,” said Dr. Michael Devoy, Head of Medical Affairs & Pharmacovigilance of Bayer AG’s Pharmaceuticals Division and Bayer Chief Medical Officer. “The current treatment approach, however, has been associated with an increased risk of bleeding. Against this background it is particularly encouraging that in comparison to the VKA treatment strategy tested in

PIONEER AF-PCI, rivaroxaban 15 mg once daily in combination with single antiplatelet therapy significantly reduced the rate of clinically significant bleeding in this patient population by 41 percent.”

AF is the most common heart rhythm condition worldwide, affecting an estimated 33.5 million people across the globe<sup>2</sup>. Of these patients, 20-40% also have coronary artery disease, exposing them to the risk of having to undergo PCI<sup>3,4</sup>. Between 5-15% of patients with AF will require a stent – through a PCI procedure – in their lifetime<sup>5</sup>. These patients are at increased risk of blood clots, which can trigger severe consequences including stroke, myocardial infarction or stent thrombosis<sup>4,6</sup>.

The positive CHMP opinion is based on data from the Phase IIIb PIONEER AF-PCI study, published in [\*The New England Journal of Medicine\*](#) in December 2016, which demonstrated that rivaroxaban 15 mg once daily in combination with single antiplatelet therapy significantly reduced the rate of clinically significant bleeding by 41 per cent (relative risk reduction; equivalent to 9.9 percent absolute risk reduction) compared to VKA plus dual antiplatelet therapy (DAPT) through 12 months of randomised therapy in these patients. The rivaroxaban treatment regimen showed similar rates for the exploratory efficacy endpoint of cardiovascular death, MI, stroke, and stent thrombosis compared to the VKA treatment regimen; however, the study was not powered for statistical significance on efficacy, and therefore no conclusions can be made regarding the efficacy outcomes.

PIONEER AF-PCI is the first randomised study of a NOAC in this patient population. It adds to the extensive investigation of rivaroxaban, which, by the time of its completion, is expected to include more than 275,000 patients in both clinical trials and real-world settings.

### **About PIONEER AF-PCI<sup>7</sup>**

PIONEER AF-PCI was an open-label, randomised Phase IIIb study, designed to determine the safety of two rivaroxaban treatment regimens versus a dose-adjusted vitamin K antagonist (VKA) treatment strategy after percutaneous coronary intervention (PCI) with stent placement in patients with non-valvular atrial fibrillation (AF). PIONEER AF-PCI included 2,124 patients worldwide in 26 different countries.

The primary endpoint of the study was the occurrence of clinically significant bleeding, defined as a composite of TIMI major bleeding, TIMI minor bleeding and bleeding

requiring medical attention through 12 months of randomised therapy. All patients were randomised in a 1:1:1 ratio into three treatment arms:

- Arm 1: Rivaroxaban 15 mg once daily (or 10 mg od for patients with moderate renal impairment [CrCl: 30 – 50 ml/min]) plus clopidogrel (or prasugrel or ticagrelor) for 12 months
- Arm 2: Rivaroxaban 2.5 mg twice daily plus a pre-specified duration of 1, 6 or 12 months (investigator determined) of DAPT consisting of low-dose acetylsalicylic acid (ASA) + clopidogrel (or prasugrel or ticagrelor), followed by rivaroxaban 15 mg once daily (or 10 mg od for patients with moderate renal impairment) in combination with low-dose ASA to end of month 12
- Arm 3: Triple therapy consisting of dose-adjusted VKA (target INR of 2.0–3.0) plus DAPT (as in arm 2) for a pre-specified duration of 1, 6 or 12 months (investigator determined), followed by dose-adjusted VKA (target INR of 2.0–3.0) in combination with low-dose ASA to end of month 12

PIONEER AF-PCI demonstrated that rivaroxaban 15 mg once-daily plus clopidogrel significantly reduced the rate of clinically significant bleeding by 41 percent (relative risk reduction) compared with triple therapy consisting of a VKA in combination with dual antiplatelet therapy (DAPT) (16.8% vs 26.7%; HR 0.59; 95% CI 0.47-0.76;  $p < 0.001$ ) through 12 months of randomised therapy. Rivaroxaban 2.5 mg twice-daily in combination with DAPT reduced the rate of clinically significant bleeding compared to VKA + DAPT by 37 percent (relative risk reduction) through 12 months of randomised therapy, which was also statistically significant (18.0% vs 26.7%; HR 0.63; 95% CI 0.50-0.80;  $p < 0.001$ ). The rivaroxaban treatment regimens showed similar rates for the exploratory efficacy endpoint of cardiovascular death, MI, stroke, and stent thrombosis compared to the VKA treatment regimen; however, the study was not powered for statistical significance on efficacy, and therefore no conclusions can be made regarding the efficacy outcomes.

Additionally, a separate sub-analysis of PIONEER AF-PCI, published in November 2016 in *Circulation*, showed that both rivaroxaban treatment regimens resulted in significantly lower rates of all-cause mortality or recurrent hospitalisation due to adverse events (bleeding, a cardiovascular cause or other cause) than the VKA treatment strategy. The risk of all-cause mortality or recurrent hospitalisation was 34.9 per cent in the rivaroxaban 15 mg once-daily group ( $p = 0.008$ ) and 31.9 percent in the rivaroxaban 2.5 mg twice-daily group ( $p = 0.002$ ) compared to 41.9 percent in the VKA group. When looking specifically at

re-hospitalisation, both rivaroxaban treatment groups had significantly lower rates of all-cause re-hospitalisation, with 34.1 percent in the rivaroxaban 15 mg once-daily group ( $p=0.005$ ) and 31.2 percent in the rivaroxaban 2.5 mg twice-daily group ( $p=0.001$ ) compared to 41.5 percent in the VKA group.

### **About Xarelto<sup>®</sup> (Rivaroxaban)**

Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) and is marketed under the brand name Xarelto<sup>®</sup>. 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, please visit <https://prescribe.xarelto.com>

To learn more about thrombosis, please visit [www.thrombosisadviser.com](http://www.thrombosisadviser.com)

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## **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](http://www.bayer.com).

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**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](http://www.bayer.com). The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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<sup>1</sup> C. Michael Gibson, M.D. et al. N Engl J Med 2016; 375:2423-2434

<sup>2</sup> Chugh SS, Havmoeller R, Narayanan K, et al. Arrhythmia/Electrophysiology. Circulation. 2014; 129-837-847

<sup>3</sup> The AFFIRM Investigators. Baseline characteristics of patients with atrial fibrillation: the AFFIRM Study. American Heart Journal 2002;143:991–1001

<sup>4</sup> Carpodanno D, Angiolillo DJ. Management of Antiplatelet and Anticoagulant Therapy in Patients With Atrial Fibrillation in the Setting of Acute Coronary Syndromes or Percutaneous Coronary Interventions. Circulation: Cardiovascular Interventions 2014;7:113–124

<sup>5</sup> Kirchhof P, Benussi S, Kotecha D, et al. Eur Heart J 2016;doi:10.1093/eurheartj/ehw210

<sup>6</sup> Sherwood et al. JACC Cardiovasc Interv. 2016 Aug 22;9(16):1694-702

<sup>7</sup> C. Michael Gibson, M.D. et al. N Engl J Med 2016; 375:2423-2434