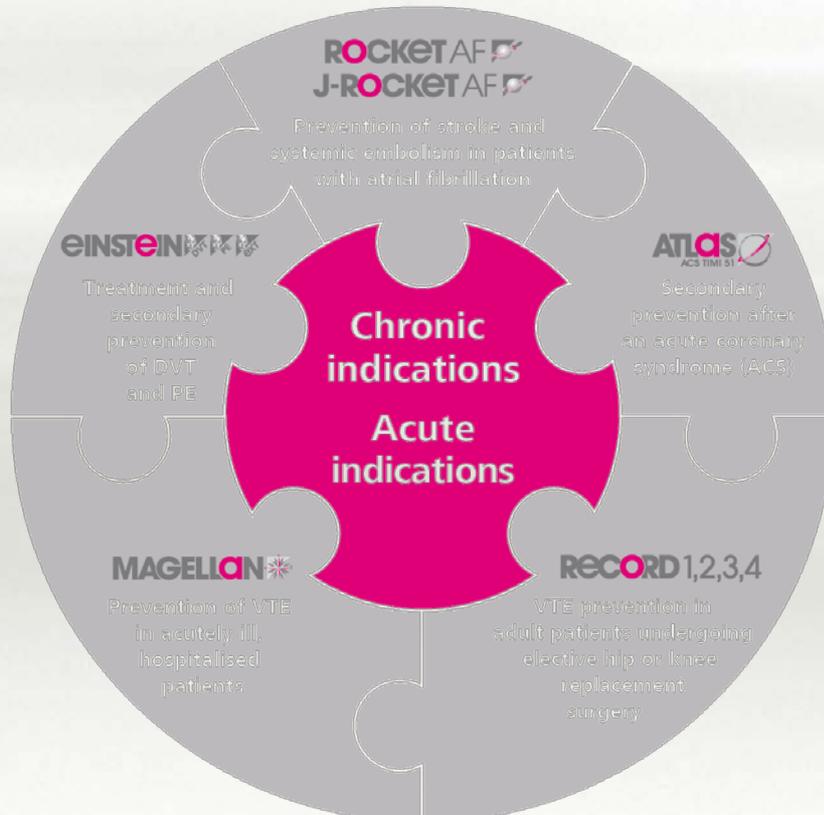


# The Xarelto® (Rivaroxaban) Clinical Trial Programme

## What is the 'Xarelto' Clinical Trial Programme?

- ◆ The extensive clinical trial programme supporting 'Xarelto' makes it the most studied and widely published novel oral anticoagulant (OAC) in the world today
- ◆ The 'Xarelto' clinical development programme includes studies that involve nearly 100,000 patients for the prevention and treatment across a broad range of venous and arterial thromboembolic (VAT) conditions, including:
  - Prevention of venous thromboembolism (VTE) in adult patients undergoing total elective hip or knee replacement surgery
  - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE
  - Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF)
  - Prevention of VTE in acutely ill, hospitalised patients
  - Secondary prevention after an acute coronary syndrome (ACS)

## Extensive Phase III Programme



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Indication	Study Programme	Patients	Primary Endpoints	Outcome
Primary prevention of VTE: Hip Replacement Surgery NCT00329628 and NCT00332020		4,541	Efficacy; composite of any: ♦ Deep vein thrombosis (DVT) ♦ Non-fatal pulmonary embolism (PE) ♦ All-cause mortality	Superior efficacy*, comparable safety <i>NEJM</i> , 2008 <sup>1</sup>
		2,509		Superior efficacy**, comparable safety <i>The Lancet</i> , 2008 <sup>2</sup>
Primary prevention of VTE: Knee Replacement Surgery NCT00361894 and NCT00362232		2,531	Safety: ♦ Major bleeding  Comparator: ♦ Enoxaparin	Superior efficacy*, comparable safety <i>NEJM</i> , 2008 <sup>3</sup>
		3,148		Superior efficacy*, comparable safety <i>The Lancet</i> , 2009 <sup>4</sup>
VTE Prevention: Acutely ill, Hospitalised Patients NCT00571649		8,101	Efficacy; composite of: ♦ Asymptomatic proximal DVT ♦ Symptomatic DVT ♦ Non-fatal PE and VTE-related death  Safety: ♦ Composite of major and non-major clinically relevant bleeding  Comparator: ♦ Enoxaparin	Primary efficacy endpoints met, but no consistent positive benefit-risk balance  Results presented at ACC, 2011 <sup>5</sup>
Treatment of Deep Vein Thrombosis (DVT) NCT00440193		3,449	Efficacy: ♦ Symptomatic recurrent VTE – the composite of recurrent DVT, fatal or non-fatal PE	Non-inferior efficacy, comparable safety <i>NEJM</i> , 2010 <sup>6</sup>
Treatment of Pulmonary Embolism (PE) NCT00439777		4,833	Safety: ♦ DVT & PE: Clinically relevant bleeding – the composite of major or clinically relevant non-major bleeding ♦ EXT: Major bleeding events	Non-inferior efficacy, comparable safety, significantly lower rate of major bleeding <i>NEJM</i> , 2012 <sup>7</sup>
Secondary Prevention of Venous Thrombo-embolism (VTE) NCT00439725		1,197	Comparator: ♦ DVT & PE: Enoxaparin followed by a vitamin k antagonist (VKA) ♦ EXT: Placebo	Superior efficacy***, comparable safety with low major bleeding rates <i>NEJM</i> , 2010 <sup>6</sup>

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Indication	Study Programme	Patients	Primary Endpoints	Outcome
<b>Prevention of Stroke and Systemic Embolism in Patients with Non-valvular Atrial Fibrillation (AF)</b> NCT00403767		14,264	Efficacy; composite of: ♦ Stroke ♦ Non-CNS systemic embolism  Safety; composite of: ♦ Major and non-major clinically relevant bleeding events  Comparator: ♦ Warfarin	Primary efficacy endpoints met; non-inferiority****  Similar overall bleeding rates with significantly fewer fatal bleeds and intracranial haemorrhages***** <i>NEJM</i> , 2011 <sup>8</sup>
<b>Prevention of Stroke and Systemic Embolism in Patients with Non-valvular Atrial Fibrillation (AF)</b> NCT00403767		1,280	Safety; composite of: ♦ Major and non-major clinically relevant bleeding events  Comparator: ♦ Warfarin	Primary endpoint met, non-inferiority for the principal safety outcome  Similar bleeding with a trend to fewer fatal bleeding events and intracranial haemorrhages <i>CJ</i> , 2012 <sup>9</sup>
<b>Secondary Prevention after an Acute Coronary Syndrome (ACS)</b> NCT00402597		15,526	Efficacy; composite of: ♦ CV death, MI, or stroke  Safety; composite of: ♦ Major TIMI bleeding not related to CABG  Comparator: ♦ Placebo	Primary efficacy endpoint met; significant risk reduction in composite of CV death, MI and stroke  Significantly increased major bleeding; importantly, the rates of fatal bleeding were low and similar across all groups <i>NEJM</i> 2011 <sup>10</sup>

\* Superiority vs. enoxaparin

\*\* Extended duration with rivaroxaban more effective than short-term therapy with enoxaparin

\*\*\* Superiority vs. placebo

\*\*\*\* Non-inferiority vs. warfarin; among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71)

\*\*\*\*\* Mucosal bleeding events were seen more frequently with rivaroxaban compared with warfarin.

Patients on rivaroxaban had significant increases in the following major bleeding events: a  $\geq 2$  g/dL fall in haemoglobin (2.8%/yr vs 2.3%/yr P=0.019) and transfusions (1.7%/yr vs 1.3%/yr P=0.044)

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## Real-world, Non-interventional Studies

As an extension to the 'Xarelto' Clinical Trial Programme, a number of real-world studies are designed to observe and further evaluate 'Xarelto' in everyday clinical practice.

- ◆ In April 2012, results from XAMOS reaffirmed the findings from RECORD that 'Xarelto' is safe and effective in protecting patients from VTE blood clots following elective total hip or knee replacement surgery

Indication	Study Programme	Patients	Primary Outcome Measures	Outcome
<p>Primary prevention of VTE: Hip and Knee Replacement Surgery NCT00831714</p>		17,413	<ul style="list-style-type: none"> <li>◆ Outcomes were reported as serious or non-serious adverse events, and all events were analysed in the safety population</li> <li>◆ Arterial and venous thromboembolic events, including symptomatic thromboembolic events (DVT, PE)</li> <li>◆ Bleeding events</li> <li>◆ Other adverse events</li> <li>◆ All-cause mortality</li> </ul>	<p>Lower incidence of symptomatic thromboembolic events</p> <p>Low and similar rates of major bleeding in both study groups</p> <p>Results presented at BSH, 2012<sup>11</sup></p>

**Ongoing Studies:** Continually evaluating the efficacy and safety of 'Xarelto' across more venous and arterial diseases

### Clinical Development Studies:

- ◆ COMPASS will assess the potential use of 'Xarelto' in combination with aspirin, or as a single treatment to prevent major adverse cardiac events (MACE) in nearly 20,000 patients with atherosclerosis related to coronary or peripheral artery disease (CAD or PAD), in 29 countries
- ◆ COMMANDER-HF will evaluate the potential added benefit of rivaroxaban in combination with single or dual-antiplatelet therapy to help reduce the risk of death, heart attack and stroke in approximately 5,000 patients with chronic heart failure (HF) and coronary artery disease (CAD), following hospitalisation for exacerbation of their HF

### Interventional Clinical Studies:

- ◆ X-VerT will further examine the efficacy and safety of 'Xarelto' in comparison to dose-adjusted vitamin K antagonist (VKA) in preventing cardiovascular events, including stroke, in approximately 1,500 patients with AF scheduled for cardioversion
- ◆ VENTURE-AF will evaluate the safety profile of Xarelto in patients with non-valvular AF undergoing first catheter ablation, in 200 patients across five countries

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## Non-Interventional Studies:

- ◆ XANTUS is designed to collate data on real-world protection with 'Xarelto' in over 6,000 adult patients in Europe with non-valvular AF at risk of stroke
- ◆ XANAP is designed to collate data on real-world protection with 'Xarelto' in over 5,000 adult patients in Europe and Asia with non-valvular AF at risk of stroke
- ◆ XALIA will generate information from over 4,800 patients treated for an acute DVT with either 'Xarelto' or standard of care

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## About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, 'Xarelto' is approved for five indications across seven distinct areas of use, consistently protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other novel OAC:

- 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 deep vein thrombosis (DVT) in adults
- The treatment of pulmonary embolism (PE) in adults
- The prevention of recurrent DVT and PE in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of venous thromboembolism (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 when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine)

Whilst licences may differ from country to country, across all indications 'Xarelto' is approved in more than 120 countries.

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. 'Xarelto' is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

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 high priority for Bayer, and the company has developed a [Prescribers Guide](#) for physicians and a [Xarelto Patient Card](#) for patients to support best practices. To learn more, please visit: <https://prescribe.xarelto.com>.

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

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

To learn more about 'Xarelto', please visit [www.xarelto.com](http://www.xarelto.com)

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