

# The ATLAS Clinical Study Programme

## What is the ATLAS Clinical Study Programme?

- ◆ The ATLAS ACS (**A**nti-Xa **T**herapy to **L**ower cardiovascular events in addition to aspirin with/without thienopyridine therapy in subjects with **A**cute **C**oronary **S**yndrome) clinical studies were global Phase II and Phase III trials involving 19,018 patients, evaluating the safety and efficacy of Xarelto® (rivaroxaban) in patients with recently diagnosed ACS receiving standard antiplatelet therapy
- ◆ The purpose of the ATLAS ACS studies was to determine whether 'Xarelto' in addition to standard care reduces the risk of the composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke in subjects with a recent ACS event, compared with placebo, with an acceptable risk of bleeding events
- ◆ The ATLAS ACS clinical trial programme was conducted in collaboration with the Thrombolysis in Myocardial Infarction (TIMI) Study Group
  - **ATLAS ACS-TIMI 46** was a double-blind, dose-escalation Phase II study of 'Xarelto' in the secondary prevention of ACS in patients who are treated with aspirin alone or aspirin plus a thienopyridine
  - **ATLAS ACS-TIMI 51** was an international Phase III clinical trial, involving 15,526 patients hospitalised with ACS and was designed to test the efficacy of 'Xarelto' compared to placebo in preventing CV death, MI or stroke. Patients were given standard antiplatelet therapy plus 'Xarelto' dosed at 2.5mg BID or 5mg BID, or placebo. Of the patients randomised into the study, 93% received aspirin and thienopyridine in addition to 'Xarelto' or placebo, and the balance were treated with aspirin plus 'Xarelto' or placebo

## ATLAS ACS-TIMI 46 Results: Summary

- ◆ In the Phase II ATLAS ACS TIMI 46 study, 'Xarelto', when taken in combination with antiplatelet therapy, was associated with a 21% relative risk reduction for its primary efficacy endpoint and a 31% relative risk reduction against its secondary endpoint of a composite of CV death, MI or stroke
- ◆ As expected, 'Xarelto'-treated patients exhibited dose-dependent increases in bleeding vs. placebo when administered on a background of antiplatelet therapy. However, no study arm was halted due to increased bleeding





## ATLAS ACS-TIMI 51 Results: Summary

- ◆ The results of the ATLAS ACS-TIMI 51 study showed that both 2.5 and 5 mg of 'Xarelto' dosed twice daily (BID) in addition to standard therapy — low-dose aspirin with or without a thienopyridine such as clopidogrel — were superior to standard therapy plus placebo in both study arms in the primary efficacy endpoint of preventing recurrent major cardiovascular events (cardiovascular death, myocardial infarction or stroke) in patients with ACS [combined doses 8.9% vs. 10.7% (P=0.008), Relative Risk Reduction (RRR)=16%]. Additionally and importantly, 'Xarelto' significantly reduced stent thrombosis compared with placebo [2.3% vs. 2.9% (P=0.016)]
- ◆ Patients dosed with 2.5 mg BID of 'Xarelto' showed a significant reduction in risk of the composite primary endpoint [9.1% vs. 10.7% (P=0.020)], driven by a significant 34% RRR in the rate of cardiovascular death [2.7% vs. 4.1% (P=0.002)]. There was also a significant reduction in deaths from any cause [4.5% to 2.9% (P=0.002)]. The 5 mg BID dose of 'Xarelto' also reduced the rate of the primary efficacy endpoint in the study [8.8% vs. 10.7% (P=0.028)]
- ◆ The principal safety endpoint for the study was TIMI major bleeding not associated with coronary artery bypass graft (CABG) surgery. In patients receiving 'Xarelto' in combination with standard therapy, bleeding rates were low overall, yet statistically significantly increased versus those treated with standard therapy plus placebo [2.1% vs. 0.6% (p<0.001)]
  - Similarly, 'Xarelto' resulted in higher rates of TIMI major bleeding events not associated with CABG surgery at both the 2.5mg and 5mg BID doses compared to placebo [1.8% vs. 0.6% (p<0.001)] and 2.4% vs. 0.6% (p<0.001), respectively
  - Importantly, the rates of fatal bleeding (including fatal intracranial haemorrhages) were low and similar across all groups
  - Other treatment-emergent adverse events were generally balanced across treatment groups
- ◆ Full data from ATLAS ACS-TIMI 51 were presented on 13 November 2011 at the American Heart Association (AHA) Scientific Sessions meeting in Orlando, FL, USA



## ATLAS: Study Design and Results

<b>ATLAS ACS-TIMI 46 Study<sup>1</sup></b>	
<b>Study design</b>	<ul style="list-style-type: none"> <li>◆ Multi-centre, randomized, double-blind, parallel-group, Phase II dosing and safety study</li> <li>◆ Pre-defined study period of 6 months</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>◆ Stratum 1: Low-dose aspirin and either:               <ul style="list-style-type: none"> <li>● One of three doses of 'Xarelto' (5 mg, 10 mg, or 20 mg) taken once daily</li> <li>● Twice-daily 'Xarelto' with total daily amount equaling (5 mg, 10 mg, or 20 mg)</li> <li>● Placebo</li> </ul> </li> <li>◆ Stratum 2: Low-dose aspirin and a thienopyridine, such as clopidogrel and either:               <ul style="list-style-type: none"> <li>● One of four doses of 'Xarelto' (5 mg, 10 mg, 15 or 20 mg) taken once-daily</li> <li>● Twice-daily 'Xarelto' with total daily amount equaling (5 mg, 10 mg, 15 or 20 mg)</li> <li>● Placebo</li> </ul> </li> </ul>
<b>Number of patients</b>	◆ 3,491 patients from 297 sites in 27 countries
<b>Primary efficacy endpoint</b>	◆ Composite of death, MI, stroke or severe recurrent ischaemia requiring revascularization up to 6 months post enrolment
<b>Secondary efficacy endpoint</b>	◆ Composite of death, MI or stroke up to 6 months post enrolment
<b>Primary safety endpoint</b>	◆ Clinically significant bleeding (TIMI major, TIMI minor, or bleeding requiring medical attention)
<b>RESULTS</b>	
<b>Primary efficacy endpoint</b>	◆ Compared with placebo, 'Xarelto' tended to reduce the primary efficacy endpoint of death, myocardial infarction, stroke, or severe recurrent ischaemia requiring revascularisation across the entire population from 7.0% to 5.6% (HR 0.79, 95% CI 0.60-1.05, P=0.10), however, no statistically significant difference was shown
<b>Secondary efficacy endpoint</b>	◆ 'Xarelto' compared with placebo was associated with a significant reduction in the secondary endpoint, the composite of death, MI, or stroke by 31% (from 5.5% to 3.9%, HR 0.69, 95% CI 0.50-0.96, P=0.03)
<b>Primary safety endpoint</b>	<ul style="list-style-type: none"> <li>◆ Similar bleeding compared to the standard of care [8.1% in both treatment groups (p=0.77)]</li> <li>◆ 'Xarelto' was associated with clinically significant major bleeding, which increased in a dose dependant fashion</li> <li>◆ TIMI major bleeding increased vs. placebo in:               <ul style="list-style-type: none"> <li>● 'Aspirin' only stratum: 0.0% to 1.2% (p=0.17)</li> <li>● 'Aspirin' + clopidogrel stratum: 0.2% to 1.2% (p=0.03)</li> </ul> </li> </ul>



<b>ATLAS ACS-TIMI 51 Study<sup>2,3</sup></b>	
<b>Study design</b>	<ul style="list-style-type: none"> <li>◆ Multi-centre, randomized, event-driven, double-blind, parallel-group, placebo controlled study</li> <li>◆ Conducted in 44 countries and at 766 sites worldwide</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>◆ Stratum 1: Standard antiplatelet therapy of low-dose aspirin and either:               <ul style="list-style-type: none"> <li>● One of two doses of oral 'Xarelto' (2.5 mg and 5 mg) taken twice daily</li> <li>● Placebo</li> </ul> </li> <li>◆ Stratum 2: Low-dose aspirin and a thienopyridine, such as clopidogrel and either:               <ul style="list-style-type: none"> <li>● One of two doses of oral 'Xarelto' (2.5 mg and 5 mg) taken twice-daily</li> <li>● Placebo</li> </ul> </li> </ul>
<b>Number of patients</b>	◆ 15,526 patients worldwide
<b>Primary efficacy endpoint</b>	◆ Reduction in the risk of the composite of CV death, MI or stroke
<b>Primary safety endpoint</b>	◆ TIMI major bleeding events not associated with coronary artery bypass graft (CABG) surgery
<b>RESULTS</b>	
<b>Primary efficacy endpoint</b>	<ul style="list-style-type: none"> <li>◆ 'Xarelto' met its primary efficacy endpoint with significant reductions in the rates of CV death, MI and stroke</li> <li>◆ In both strata, 'Xarelto' 2.5 mg BID in addition to antiplatelet therapy showed:               <ul style="list-style-type: none"> <li>● A significant 16% RRR in the composite of CV death, MI and stroke: HR 0.84 (0.72-0.97) p=0.020</li> <li>● A significant 34% RRR in cardiovascular mortality: 2.7 vs 4.1%; HR 0.66 (95% CI 0.51–0.86); p=0.002</li> <li>● A significant 32% RRR in all-cause mortality: 2.9 vs 4.5%; HR 0.68 (95% CI 0.53–0.87); p=0.002</li> </ul> </li> <li>◆ In both strata, compared with placebo, 'Xarelto' 5.0 mg BID in addition to antiplatelet therapy showed:               <ul style="list-style-type: none"> <li>● A significant 15% RRR in the composite of CV death, MI and stroke: 8.8 vs 10.7%; HR 0.85 (95% CI 0.73–0.98); p=0.028</li> </ul> </li> </ul>
<b>Primary safety endpoint</b>	<ul style="list-style-type: none"> <li>◆ There was a dose-dependent statistically significant increase in the risk of non-CABG-related TIMI major bleeding with 'Xarelto' plus standard of care compared with standard of care plus placebo: 'Xarelto' 2.5mg BID 1.8% vs. 0.6% HR 3.46 (p&lt;0.001); 'Xarelto' 5mg BID 2.4% vs. 0.6% HR 4.47 (p&lt;0.001)               <ul style="list-style-type: none"> <li>● The rate of fatal bleeding was low – 6 (0.1%) with 'Xarelto' 2.5mg BID (HR 3.46 p&lt;0.001); 15 (0.4%) with 'Xarelto' 5mg BID, and 9 (0.2%) with placebo</li> <li>● The rate of intracranial bleeding was low – 14 (0.4%) with 'Xarelto' 2.5mg BID; 18 (0.7%) with 'Xarelto' 5mg BID, and 5 (0.2%) with placebo</li> </ul> </li> </ul>

\*The TIMI scale is one of the most well-known risk scoring methods for a patient hospitalised with a heart attack. Using a patient's current vital health information as a guide, the TIMI scale provides a numeric value for the patient's potential prognosis, including short-term risk of death





## References

- 1) Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban Versus Placebo in Patients with Acute Coronary Syndromes (ATLAS ACS-TIMI 46): a randomized, double-blind, phase II trial. *Lancet*. 2009;374,(9683)29-38
- 2) Clinicaltrials.gov. An Efficacy and Safety Study for Rivaroxaban in Patients With Acute Coronary Syndrome. Available at <http://clinicaltrials.gov/ct2/show/NCT00809965?term=rivaroxaban&rank=4> Last accessed November 2011
- 3) Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N.Engl.J.Med.* 2011; [Epub ahead of print]

## About Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and a limited potential for food and drug interactions.

Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin in this indication. Rivaroxaban is approved in more than 110 countries worldwide and marketed outside the U.S. by Bayer HealthCare in this indication.

In the U.S., where rivaroxaban has been available since July 2011 for VTE prevention in adult patients following elective hip or knee replacement surgery, Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights. The Bayer HealthCare sales force is supporting Janssen Pharmaceuticals, Inc. in designated hospital accounts. On November 4, Xarelto® received further marketing approval in the U.S. for the prevention of stroke in patients with Atrial Fibrillation.

The extensive clinical trial programme supporting rivaroxaban makes it the most studied and widely published oral, direct Factor Xa inhibitor. The studies, reported and ongoing, involve over 75,000 patients for the prevention and treatment of venous and arterial thromboembolic (VAT) disorders across a broad range of acute and chronic conditions, including stroke prevention in patients with Atrial Fibrillation, DVT treatment and the prevention of recurrent DVT or PE, and the secondary prevention of Acute Coronary Syndrome.

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

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

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