ABOUT XARELTO® CLINICAL STUDIES

FAST FACTS

- Xarelto® (rivaroxaban) is a novel, oral direct Factor Xa inhibitor. On September 30, 2008, the European Commission granted marketing approval for 'Xarelto' for the prevention of venous blood clots in adult patients undergoing elective (planned) hip or knee replacement surgery. 'Xarelto' received its first marketing approval in Canada on September 15, 2008, for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip or total knee replacement surgery. 'Xarelto' was submitted in July 2008 for approval to the U.S. Food and Drug Administration (FDA). On approval, Ortho-McNeil, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will market the drug in the United States. In addition to the FDA submission, filings are under review with regulatory agencies in more than 10 other countries

- 'Xarelto' is also in advanced development in a range of indications for the prevention and/or treatment of potentially deadly blood clots

- The extensive clinical trial program for 'Xarelto' makes it the most studied oral anticoagulant in the world today. More than 60,000 patients are expected to be enrolled in the 'Xarelto' clinical development program, which will evaluate the product in the prevention and treatment of a broad range of blood-clotting disorders listed below:

RECORD: VTE prevention following elective (planned) hip or knee replacement surgery (Phase III; completed)

MAGELLAN: VTE prevention in hospitalized, medically ill patients (Phase III)

EINSTEIN: VTE treatment (Phase III)

ROCKET AF: Stroke prevention in patients with atrial fibrillation (Phase III)

ATLAS ACS TIMI 46: Secondary prevention of acute coronary syndrome (Phase II)

RECORD: Venous Blood Clot Prevention in Major Orthopedic Surgery

REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE

RECORD is a global program of four trials in more than 12,500 patients, comparing Xarelto® (rivaroxaban) and enoxaparin in the prevention of venous thromboembolism (VTE) after elective (planned) hip or knee replacement surgery.

RECORD comprised four pivotal Phase III clinical trials that compared 'Xarelto' taken as one tablet, once-daily, with subcutaneous enoxaparin.

RECORD1 and 2: total hip replacement surgery[1,2]

- RECORD1: Both treatments continued for 35+/-4 days
- RECORD2: 'Xarelto' continued for 35+/-4 days; enoxaparin for 12+/- 2 days

RECORD3 and 4: total knee replacement surgery[3,4]

- RECORD3: Both treatments continued for 12+/-2 days
- RECORD4: Both treatments continued for 12+/-2 days

'Xarelto' demonstrated superior efficacy for the primary endpoint over enoxaparin in the four RECORD trials, including head-to-head comparisons (RECORD1, 3 and 4), and a comparison of extended-duration (5 weeks) 'Xarelto' with short-duration (2 weeks) enoxaparin (RECORD2). RECORD4 was the first trial to evaluate 'Xarelto' against enoxaparin 30 mg injected subcutaneously twice-daily, which is the U.S.-approved treatment regimen for enoxaparin. In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding.

Results of a pre-specified pooled analysis of RECORD1, 2 and 3 showed that 'Xarelto' significantly reduced the composite of symptomatic VTE and all-cause mortality during the 2-week active controlled period by 56% compared with enoxaparin (0.4% versus 0.8%, respectively; odds ratio: 0.44; p<0.005) whilst maintaining a comparable safety profile.

Study design	Randomized, double-blind, parallel-group, multicentre, double-dummy
Patient numbers	> 12,500
Interventions	➢ RECORD1: Oral 'Xarelto' 10 mg once-daily for 35+/-4 days versus subcutaneous enoxaparin 40 mg once-daily 35+/-4 days ➢ RECORD2: Oral 'Xarelto' 10 mg once-daily for 35+/-4 days versus subcutaneous enoxaparin 40 mg once-daily for 12+/-2 days followed by placebo ➢ RECORD3: Oral 'Xarelto' 10 mg once-daily for 12+/-2 days versus subcutaneous enoxaparin 40 mg once-daily for 12+/-2 days ➢ RECORD4: Oral 'Xarelto' 10 mg once-daily for 12+/-2 days versus subcutaneous enoxaparin 30 mg twice-daily for 12+/-2 days ➢ In RECORD1, 2 and 3, enoxaparin was given the evening before surgery, whereas 'Xarelto' was given 6 – 8 hours after surgery. In RECORD4, both therapies were given post operatively ('Xarelto' 6 – 8 hours and enoxaparin 12 – 24 hours post operatively)
Primary efficacy endpoint	Composite of deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), all-cause mortality

Main safety endpoint	Major bleeding
Approvals and regulatory filings	'Xarelto' is a novel, oral direct Factor Xa inhibitor taken as one tablet, once-daily. On September 30, 2008, the European Commission granted marketing approval for 'Xarelto' for the prevention of venous blood clots in adult patients undergoing elective (planned) hip or knee replacement surgery. 'Xarelto' received its first marketing approval in Canada on September 15, 2008, for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip or total knee replacement surgery. On July 30, 2008, the new drug application (NDA) for 'Xarelto' was submitted to the U.S. Food and Drug Administration (FDA). Filings are also under review with regulatory agencies in more than 10 other countries

For the results of RECORD1, 2, 3 and 4, please refer to the "ABOUT RECORD STUDIES" backgrounder.

EINSTEIN: Venous Blood Clot Treatment

Evaluating oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism.

Program of three studies comparing rivaroxaban and enoxaparin plus a vitamin K antagonist in the treatment of symptomatic, and prevention of recurrent, venous blood clots in patients with acute symptomatic deep vein thrombosis (EINSTEIN-DVT) and acute symptomatic pulmonary embolism (EINSTEIN-PE). The long-term ability of rivaroxaban to prevent symptomatic, recurrent venous blood clots will be investigated in the EINSTEIN-Extension study in patients who have already completed 6 or 12 months of treatment with rivaroxaban or a vitamin K antagonist.

Study design	Randomized, open-label, parallel-group, multicenter
Patient numbers	~7,500
Interventions	➢ EINSTEIN-DVT and EINSTEIN-PE: Oral rivaroxaban 15 mg twice-daily for 3 weeks followed by 20 mg once-daily versus enoxaparin for at least 5 days (1 mg/kg twice-daily), plus vitamin K antagonist titrated to an International Normalized Ratio of 2.5 (range: 2.0 – 3.0). Both treatments given for either 3, 6, or 12 months ➢ EINSTEIN-Extension: Oral rivaroxaban 20 mg once-daily versus placebo in patients who have already completed 6 or 12 months of treatment with rivaroxaban or a vitamin K antagonist (the treatment itself is also given for 6 or 12 months)
Primary efficacy endpoint	Symptomatic, recurrent VTE – the composite of recurrent DVT, or fatal or non-fatal PE
Principle safety outcome	Combination of major and clinically relevant non-major bleeding events
Expected regulatory filing date*	2010

ROCKET AF: Stroke Prevention in Atrial Fibrillation *Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation* Major outcomes study to compare the efficacy and safety of rivaroxaban and warfarin for the prevention of stroke in patients with atrial fibrillation.	
Study design	Randomized, double-blind, parallel-group, multicenter
Patient numbers	~14,000
Interventions	➢ Oral rivaroxaban 20 mg once-daily (15 mg once-daily for those with moderate renal impairment at screening) ➢ Warfarin once-daily titrated to an International Normalized Ratio of 2.5 ➢ Both treatments given for an expected average of 18 months. The minimum treatment period is 12 months and some patients will receive treatment for over 24 months
Primary efficacy endpoint	Composite of stroke and non-CNS systemic embolism (blood clots outside of the brain)
Principle safety endpoint	Composite of major and non-major clinically relevant bleeding events
Expected regulatory filing date*	2010

MAGELLAN: VTE prevention in hospitalized, medically ill patients *Multicenter, rAndomized, parallel Group Efficacy and safety study for the prevention of VTE in hospitalized medically iLL patients comparing rivaroxabAN with enoxaparin* Phase III study comparing rivaroxaban with enoxaparin in hospitalized, medically ill patients.	
Study design	Multi-national, randomized, double-blind study
Patient numbers	~ 8,000 patients
Interventions	➢ Rivaroxaban 10 mg once-daily administered for 35+/-4 days ➢ Subcutaneous enoxaparin 40 mg once-daily administered for 10+/-4 days
Primary efficacy endpoint	Composite of asymptomatic proximal DVT detected by bilateral ultrasound, symptomatic DVT, non-fatal PE and VTE-related death
Primary safety endpoint	Major bleeding and non-major clinically relevant bleeding
Expected regulatory filing date*	2011

ATLAS ACS TIMI 46: Secondary Prevention in Acute Coronary Syndrome *Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome* Phase II dose-finding study of rivaroxaban in the secondary prevention of acute coronary syndrome in patients who are treated with aspirin alone or aspirin plus a thienopyridine (compounds such as clopidogrel, which prevent platelet aggregation).	
Study design	Randomized, double-blind, parallel-group, multicenter
Patient numbers	> 3,000 patients
Interventions	➢ Rivaroxaban daily doses of 5 mg, 10 mg, 15 mg and 20 mg either as OD or BID regimen ➢ Placebo Treatments given for 6 months
Safety endpoints	Adverse events, clinical laboratory tests, electrocardiograms, vital signs, bleeding events
Primary efficacy outcome	Combined incidence of death, MI (first or subsequent), stroke, or severe recurrent ischemia requiring revascularization in ACS patients receiving either aspirin or aspirin plus clopidogrel.
Expected regulatory filing date*	2011/2012

**Please note that these timings may be subject to change as the studies progress.*

To learn more about VTE please visit www.thrombosisadviser.com

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

References

1. Eriksson BI. N Engl J Med 2008; 358: 2765-2775.
2. Kakkar AK. Lancet 2008; 372: 1-9.
3. Lassen MR. N Engl J Med 2008; 358: 2777-2786.
4. Turpie A, Bauer K, Davidson B, et al. Comparison of rivaroxaban--an oral, direct factor Xa inhibitor--and subcutaneous enoxaparin for thromboprophylaxis after total knee replacement (RECORD4: a phase 3 study). Abstract F85 presented at European Federation of National Associations of Orthopaedics and Traumatology 2008 Annual Meeting; 29 May – 1 June, 2008; Nice, France.