RECORD

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PHASE III

The RECORD Clinical Development Programme Consisting of Four Distinct Pivotal Studies Proves Oral, Once-daily 'Xarelto' Provides Effective Protection Against Venous Thromboembolism (VTE) after Hip or Knee Joint Replacement Surgery

Oral, Once-daily 'Xarelto' Provides Superior Efficacy and Similar Safety to Injectable Enoxaparin

Broadest Novel OAC Study Programme in People Requiring Hip or Knee Replacement

Four Pivotal Phase III Studies involving >12,000 Patients

For patients undergoing hip or knee joint replacement surgery, venous thromboembolism (VTE) is a frequent and potentially fatal complication. Without VTE prevention, patients have a 40-60% risk of developing deep vein thrombosis (DVT) and up to a 30% risk of developing a pulmonary embolism (PE)[1].

Older therapies for prevention of VTE associated with orthopaedic surgery is a class of anticoagulant drugs known as low molecular weight heparins (LMWHs), such as enoxaparin. These therapies present certain drawbacks for the patient, including the inconvenience and discomfort of regular injections.

The global RECORD programme demonstrated that oral, once-daily 'Xarelto' provides superior protection against VTE after elective (planned) hip or knee replacement with similar safety compared to injectable enoxaparin[2,3].

- RECORD1 and RECORD2 evaluated 'Xarelto' in total hip replacement (THR)
- RECORD3 and RECORD4 evaluated 'Xarelto' in total knee replacement (TKR)

Study	Publication	Date
RECORD1	New England Journal of Medicine[4]	June 2008
RECORD2	The Lancet[5]	June 2008
RECORD3	New England Journal of Medicine[6]	June 2008
RECORD4	The Lancet[7]	August 2009

These four studies were the basis of the approval of 'Xarelto' for the prevention of VTE in adult patients undergoing elective hip or knee joint replacement surgery.

The extensive evaluation of rivaroxaban to protect different patient populations at risk of venous and arterial thromboembolism (VAT), makes it the most studied novel OAC in the world. Rivaroxaban (Xarelto®) is already approved for five indications in seven areas of use and its investigation - both completed and ongoing - will include more than 275,000 patients in linical trials and real world settings.

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The Study Results

RECORD 1

- 10 mg oral, once-daily 'Xarelto' demonstrated a 2.6% absolute risk reduction (ARR) in total VTE, a composite of any DVT, non-fatal PE and all cause mortality, in patients undergoing THR compared with once-daily injections of enoxaparin 40 mg[4]
- 'Xarelto' showed a comparable safety profile including low rates of major bleeding[4]
- Duration of thromboprophylaxis in both treatment arms was 35+/-4 days[4]

RECORD 2

- Extended-duration of 10 mg oral, once-daily 'Xarelto' (35+/-4 days) demonstrated a 7.3% ARR in total VTE and a comparable safety profile, including low rates of major bleeding, in patients undergoing THR compared to patients receiving short-duration therapy with once-daily injections of enoxaparin 40 mg (12+/-2 days) followed by placebo[5]

RECORD 3

- 10 mg oral, once-daily 'Xarelto' demonstrated 9.2% ARR in total VTE in patients undergoing TKR compared to once-daily injections of enoxaparin 40 mg[6]
- 'Xarelto' showed a comparable safety profile, including low rates of major bleeding[6]
- Both treatments were dosed for 12+/-2 days[6]

RECORD 4

- 10 mg oral, once-daily 'Xarelto' compared to the North American dosing regimen for enoxaparin of 30 mg injected twice daily demonstrated a 3.2% ARR in total VTE in patients undergoing TKR[7]
- 'Xarelto' showed a comparable safety profile including low rates of major bleeding[7]

RECORD 1-3

- Results of a pre-specified pooled analysis showed '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% vs. 0.8%), and was also more effective at the end of the planned medication period (0.5% vs 1.3%, respectively)[8]
- Rates of major bleeding were similar at two weeks and at the end of the planned medication period[8]

RECORD 1-4

- Results of a pre-specified pooled analysis showed that 'Xarelto' demonstrated a statistically significant risk reduction in the composite of symptomatic VTE and all-cause mortality of more than 50% compared to enoxaparin[3]
- At two weeks, major bleeding occurred in 0.3% of patients receiving 'Xarelto' versus 0.2% of patients receiving enoxaparin with composite rates of major and non-major clinically relevant bleeding occurring in 2.8% versus 2.5% of patients, respectively[3]
- These findings confirmed the results of the four individual RECORD studies[3]

References

1) Turpie AG, A Schmidt A, Kreutz R, et al. Rationale and design of XAMOS: noninterventional study of rivaroxaban for prophylaxis of venous thromboembolism after major hip and knee surgery. Vasc Health Risk Manag. 2012; 8 363-370. **2)** Xarelto [summary of product characteristics]. Berlin, Germany: Bayer Pharma AG; November 2013. **3)** Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: Pooled analysis of four studies. Thromb Haemost. 2011; 105: 444–453. **4)** Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N.Engl.J.Med. 2008; 358, (26) 2765-2775. **5)** Kakkar AK, Brenner B, Dahl OE, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008; 372, (9632) 31-39. **6)** Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N.Engl.J.Med. 2008; 358, (26) 2776-2786. **7)** Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009; 373, (9676) 1673-1680. **8)** Eriksson BI, Kakkar AK, Turpie AG, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg [Br]. 2009; 91-B: 636-44.