ABOUT RECORD STUDIES

FAST FACTS

- RECORD is an extensive, global programme of four pivotal trials involving more than 12,500 patients comparing oral, once-daily rivaroxaban, with injected enoxaparin in the prevention of venous thromboembolism (VTE) after total hip or knee replacement surgery
- RECORD1&2 evaluated rivaroxaban in total hip replacement surgery patients and RECORD3&4 evaluated rivaroxaban in total knee replacement surgery patients
- RECORD1,2& 3 were presented at the American Society of Hematology (ASH) annual meeting in December 2007
- RECORD1&3 showed superior efficacy of rivaroxaban in a head-to-head comparison with enoxaparin. Further, extended-duration rivaroxaban showed superior efficacy to short-duration enoxaparin followed by placebo (RECORD2)
- Across the studies, the risk of major bleeding with rivaroxaban was similar to enoxaparin
- RECORD4 evaluated rivaroxaban versus the North American regimen of injected enoxaparin; results will be presented at the 9th Annual Meeting of the European Federation of National Associations of Orthopaedics & Traumatology (EFORT) in Nice, France on 30 May 2008

A major global initiative

RECORD (**RE**gulation of **C**oagulation in major **O**rthopaedic surgery reducing the **R**isk of **D**VT and PE) is an extensive, global programme of four pivotal trials involving more than 12,500 patients comparing oral, once-daily rivaroxaban, with injected enoxaparin in the prevention of venous thromboembolism (VTE) after total hip or knee replacement surgery. Rivaroxaban is being jointly developed by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The four RECORD studies are randomised, double-blind trials:

- RECORD1 – Evaluated extended duration clot prevention (35 +/- 4 days) with subcutaneous enoxaparin versus rivaroxaban in patients undergoing total hip replacement surgery
- RECORD2 – Given that safety with extended-duration (35 +/- 4 days) clot prevention is an important real-world issue for clinicians, RECORD2 compared short-duration (10-14 days) enoxaparin with extended-duration rivaroxaban in the prevention of venous blood clots in patients undergoing total hip replacement surgery; it is the largest, prospective, randomised clinical trial comparing short-duration with extended-duration treatment to date in this indication
- RECORD3 – Evaluated rivaroxaban compared with injected enoxaparin in the prevention of venous blood clots in patients undergoing total knee replacement surgery (duration 10 to14 days)
- RECORD4 – Evaluated rivaroxaban 10 mg once-daily versus the North American regimen of injected enoxaparin (30 mg twice-daily dosing for 10 to 14 days) in patients undergoing total knee replacement surgery

Design of studies

Based on preclinical data and extensive Phase II studies that tested a wide dosing range of rivaroxaban in the prevention of venous blood clots, the once-daily 10 mg dose was found to be effective with a good safety profile. Therefore, the 10 mg once-daily dose was selected for the Phase III rivaroxaban venous blood clots prevention programme. The positive RECORD1, 2 and 3 results support this choice of dose.

RECORD1[1]	
Results show that extended prophylaxis with rivaroxaban had a significantly lower rate of venous blood clots compared to extended enoxaparin in patients following total hip replacement surgery	
Study design	Randomised, double-blind, parallel-group, multicentre
Interventions	Oral, once-daily rivaroxaban 10 mg started 6 – 8 hours after surgery Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery Both regimens continued for 35 ± 4 days
Number of patients	4541 patients undergoing total hip replacement surgery
Primary efficacy endpoint	Composite of deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - DVT (any, proximal and distal) - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS	
Primary efficacy endpoint	Rivaroxaban reduced relative risk by **70%**, $p < 0.001$ 1.1% (18/1595) rivaroxaban patients versus 3.7% (58/1558) enoxaparin patients
Major VTE	Rivaroxaban reduced relative risk by **88%**, $p < 0.001$ 0.2% (4/1686) rivaroxaban patients versus 2.0% (33/1678) enoxaparin patients
Major bleeding	0.3% rivaroxaban patients 0.1% enoxaparin patients, $p = 0.178$
Non-major bleeding	5.8% rivaroxaban patients 5.8% enoxaparin patients, $p = 1.000$

RECORD2[2]	
Results show that extended-duration rivaroxaban had significantly lower rate of venous blood clots compared to short-duration enoxaparin in patients following total hip replacement surgery	
Study design	Randomised, double-blind, parallel-group, multicentre
Interventions	Oral, once-daily rivaroxaban 10 mg started 6 – 8 hours after surgery, continued for 35+/-4 days Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery, continued for 12+/-2 days, followed by placebo
Number of patients	2509 patients undergoing total hip replacement surgery
Primary efficacy endpoint	Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death. - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS*	
Primary efficacy endpoint	Rivaroxaban reduced relative risk by **79%**, p < 0.001 2.0% (17/864) rivaroxaban patients versus 9.3% (81/869) enoxaparin patients
Major VTE	Rivaroxaban reduced relative risk by **88%**, p < 0.001 0.6% (6/961) rivaroxaban patients versus 5.1% (49/962) enoxaparin patients
Symptomatic VTE	Rivaroxaban reduced relative risk by **80%**, p = 0.004 0.2% (3/1212) rivaroxaban patients versus 1.2% (15/1207) enoxaparin patients
Major bleeding	< 0.1% rivaroxaban patients < 0.1% enoxaparin patients, p = 0.980
Non-major bleeding	6.5% rivaroxaban patients 5.5% enoxaparin patients, p = 0.246

* Comparison of short-duration enoxaparin with extended-duration rivaroxaban

RECORD3[3]	
Results show that rivaroxaban had significantly lower rate of venous blood clots compared to enoxaparin in patients following total knee replacement surgery	
Study design	Randomised, double-blind, parallel-group, multicentre
Interventions	Oral, once-daily rivaroxaban 10 mg started 6 – 8 hours after surgery Subcutaneous, once-daily enoxaparin 40 mg started the evening before surgery Both regimens continued for 13+/-4 days
Number of patients	2531 patients undergoing total knee replacement surgery
Primary efficacy endpoint	Composite of DVT, non-fatal PE, all-cause mortality
Secondary efficacy endpoints	- Major VTE: composite of proximal DVT, non-fatal PE and VTE-related death - Symptomatic VTE
Safety endpoints	Major bleeding / non-major bleeding
RESULTS	
Primary efficacy endpoint	Rivaroxaban reduced relative risk by **49%**, p < 0.001 9.6% (79/824) rivaroxaban patients versus 18.9% (166/878) enoxaparin patients
Major VTE	Rivaroxaban reduced relative risk by **62%**, p = 0.016 1.0% (9/908) rivaroxaban patients versus 2.6% (24/925) enoxaparin patients
Symptomatic VTE	Rivaroxaban reduced relative risk by **66%**, p = 0.005 0.7% (8/1201) rivaroxaban patients versus 2.0% (24/1217) enoxaparin patients
Major bleeding	0.6% rivaroxaban patients 0.5% enoxaparin patients, p = 0.774
Non-major bleeding	4.3% rivaroxaban patients 4.4% enoxaparin patients, p = 0.990

References

1. Eriksson BI, Borris LC, Friedman RJ, et al. Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: the RECORD1 trial. Abstract 2367 presented at American Society of Hematology 49th Annual Meeting in Atlanta, Georgia, 8 – 11 December, 2007.
2. Kakkar AK, Brenner B, Dahl OE, et al. Extended thromboprophylaxis with rivaroxaban compared with short-term thromboprophylaxis with enoxaparin after total hip arthroplasty: the RECORD2 trial. Abstract 307 presented at American Society of Hematology 49th Annual Meeting in Atlanta, Georgia, 8 – 11 December, 2007.
3. Lassen MR, Turpie AG, Rosencher N, et al. Rivaroxaban – an oral, direct Factor Xa inhibitor – for thromboprophylaxis after total knee arthroplasty: the RECORD3 trial. Abstract 308 presented at American Society of Hematology 49th Annual Meeting in Atlanta, Georgia, 8 – 11 December, 2007.