About RECORD Studies

A Major Global Initiative

RECORD (**RE**gulation of **C**oagulation in major **O**rthopedic surgery reducing the **R**isk of **D**VT and PE) is an extensive global program of four pivotal trials in more than 12,000 patients comparing oral, once-daily rivaroxaban, with subcutaneous enoxaparin in the prevention of venous thromboembolism (VTE) after major orthopedic surgery of the lower limbs. Rivaroxaban is being jointly developed by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

RECORD1, 2 and 3 have consistently demonstrated superior efficacy for oral, once-daily rivaroxaban compared to subcutaneous enoxaparin, the current standard of care, in the prevention of venous blood clots after major orthopedic surgery of the lower limbs. Overall, rivaroxaban has been shown to outperform enoxaparin in three Phase III studies of the prevention of venous blood clots in patients undergoing major orthopedic surgery, with a similarly rate of bleeding. In addition, the studies showed clinically meaningful results in favor of rivaroxaban in reducing symptomatic venous blood clots, i.e., those that are accompanied by clinical signs or symptoms.[1–3]

Unmet Needs in VTE Prevention

Venous blood clots are considered the most frequent, preventable, serious and potentially fatal complication following major orthopedic surgery. Venous blood clots occur in more than 50% of patients undergoing major orthopedic surgery who do not receive preventative care.[4]

Current anticoagulants have a number of limitations, such as the need for injections and non-specific mechanism of action. The development of rivaroxaban has been guided by the need for anticoagulants that specifically target a pivotal point in the blood clotting cascade to prevent blood clotting over a broad range of doses. This may eliminate the need for routine blood monitoring and dose adjustments.

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 program. The positive RECORD1, 2 and 3 results support this choice of dose, demonstrating superior efficacy of rivaroxaban over enoxaparin in the prevention of venous blood clots in patients undergoing major orthopedic surgery of the lower limbs with a similarly low rate of major bleeding.

The four RECORD studies are all randomized, double-blind trials in either total hip replacement (RECORD1 and 2) or total knee replacement (RECORD3 and 4) surgery:

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

Key Findings

Data from RECORD1, 2 and 3 were presented at the 49th Annual Meeting of the American Society of Hematology in Atlanta, Georgia, from 8–11 December 2007. Results from the RECORD3 study were initially presented at the International Society on Thrombosis and Hemostasis Congress in July 2007. The RECORD4 study is currently ongoing with results anticipated in 2008.

Overall data from RECORD1, 2 and 3 have consistently demonstrated superior efficacy for oral, once-daily rivaroxaban compared to enoxaparin, with a similarly low rate of bleeding:

- RECORD1 and 3 results show superior efficacy of rivaroxaban over enoxaparin in the prevention of venous blood clots in patients undergoing total hip or knee replacement surgery, with a similarly rate of bleeding.
- RECORD2 further demonstrates that extended-duration rivaroxaban was more effective than short-term enoxaparin followed by placebo, with a similar safety profile.
- A key secondary endpoint of the study measuring the reduction of symptomatic VTE, showed clinically meaningful results in favor of rivaroxaban. RECORD1 showed an RRR of 45%, an 80% RRR was observed in RECORD2 and a 66% RRR in RECORD3, compared to the standard regimen.

Further details on the results of RECORD1, 2 and 3 are given below:

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	Randomized, double-blind, parallel-group, multicenter
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 5 weeks
Number of patients	4541 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 **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
Symptomatic VTE	Rivaroxaban reduced relative risk by **45%*** 0.3% (6/2193) rivaroxaban patients versus 0.5% (11/2206) enoxaparin patients. *Note: this result was not statistically significant
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 rivaroxaban had significantly lower rate of venous blood clots compared to short-term enoxaparin in patients following total hip replacement surgery	
Study design	Randomized, double-blind, parallel-group, multicenter
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

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	Randomized, double-blind, parallel-group, multicenter
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

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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.
4. Choi BY. J Surg Orthop Adv 2007; 16: 31–5.