Bayer HealthCare

About Rivaroxaban Clinical Studies

Rivaroxaban is a novel, oral, once-daily direct Factor Xa inhibitor in advanced clinical development for a range of patients who could benefit from the prevention and/or treatment of blood clots.

To date, rivaroxaban is the most studied oral, direct Factor Xa inhibitor in development. More than 20,000 patients have been evaluated in the completed Phase II programs and enrolled thus far in the Phase III programs. Almost 50,000 patients are expected to be enrolled into the rivaroxaban clinical development program which will evaluate rivaroxaban in the prevention and treatment of a broad range of acute and chronic blood-clotting disorders listed below:

- **RECORD:** VTE prevention in orthopedic surgery 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* Global program of four pivotal trials comparing rivaroxaban and enoxaparin in the prevention of venous blood clots after elective, major orthopedic surgery. RECORD1 and 2: total hip replacement surgery RECORD3 and 4: total knee replacement surgery	
Study design	Randomized, double-blind, parallel-group, multicenter
Patient numbers	> 12,000
Interventions	➢ Oral rivaroxaban 10 mg once-daily for 5 weeks (RECORD1 and 2) or 10–14 days (RECORD3 and 4) ➢ Subcutaneous enoxaparin 40 mg once-daily for 5 weeks (RECORD1) or 10–14 days (RECORD2 and 3); enoxaparin 30 mg twice-daily for 10–14 days (RECORD4) ➢ In RECORD1, 2 and 3 enoxaparin was given the evening before surgery, whereas rivaroxaban was given 6–8 hours after surgery. In RECORD4, both therapies are being given post-operatively
Primary efficacy endpoints	Composite of deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), all-cause mortality
Primary safety endpoints	Major bleeding Clinically relevant non-major bleeding
Expected regulatory filing date*	Regulatory filing submitted in the EU in October 2007, planned in the US in 2008

For the results of RECORD1, 2 and 3, please refer to the RECORD Studies backgrounder.

EINSTEIN-DVT and EINSTEIN-PE: Venous Blood Clot Treatment Evaluating oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism. Program of two 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).	
Study design	Randomized, open-label, parallel-group, multicenter
Patient numbers	~6,200
Interventions	➢ Oral rivaroxaban 15 mg twice-daily for 3 weeks followed by 20 mg once-daily ➢ 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
Primary efficacy endpoints	Symptomatic, recurrent venous blood clots – the composite of recurrent DVT, or fatal or non-fatal PE
Primary safety endpoints	Composite of major and non-major clinically relevant bleeding events
Expected regulatory filing date*	2010

EINSTEIN Extension: Venous Blood Clot Treatment Evaluating oral, direct Factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep vein thrombosis or pulmonary embolism. 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, double-blind, parallel-group, multicenter
Patient numbers	~1,300
Interventions	➢ Oral rivaroxaban 20 mg once-daily ➢ Placebo Both treatments given for 6 or 12 months
Primary efficacy endpoints	Symptomatic, recurrent venous blood clots – the composite of recurrent DVT, or fatal and non-fatal PE
Primary safety endpoints	Composite of major and non-major clinically relevant 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 antagonism 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.	
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 endpoints	Composite of stroke and non CNS systemic embolism (blood clots outside of the brain)
Primary safety endpoints	Composite of major and non-major clinically relevant bleeding events
Expected regulatory filing date*	2010

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 2.5 to 15 mg twice-daily; or 5 to 30 mg once-daily ➢ Placebo Treatments given for 6 months
Primary endpoints	Selection of optimal dose
Safety endpoints	Adverse events, clinical laboratory tests, electrocardiograms, vital signs, bleeding events
Expected regulatory filing date*	TBC

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