Bayer HealthCare

ABOUT RIVAROXABAN CLINICAL STUDIES

FAST FACTS

- Rivaroxaban is an 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 potentially deadly 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 overall 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 total hip and knee replacement surgery patients (Phase III)

EINSTEIN: VTE treatment (Phase III)

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

MAGELLAN: VTE prevention in hospitalized, medically ill patients (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 programme of four pivotal trials comparing rivaroxaban and enoxaparin in the prevention of venous blood clots after total hip or knee replacement surgery.
RECORD1 and 2: total hip replacement surgery

- RECORD1: Both treatments continued for 5 weeks
- RECORD2: Rivaroxaban continued for 5 weeks; enoxaparin 10-14 days

RECORD3 and 4: total knee replacement surgery

- RECORD3: Both treatments continued for 10-14 days
- RECORD4: Both treatments continued for 10–14 days

Study design	Randomised, double-blind, parallel-group, multicentre
Patient numbers	> 12,500
Interventions	➢ RECORD1: Oral rivaroxaban 10 mg once-daily for 5 weeks versus subcutaneous enoxaparin 40 mg once-daily for 5 weeks ➢ RECORD2: Oral rivaroxaban 10 mg once-daily for 5 weeks versus subcutaneous enoxaparin 40 mg once-daily for 10–14 days followed by placebo ➢ RECORD3: Oral rivaroxaban 10 mg once-daily for 10–14

	days versus subcutaneous enoxaparin 40 mg once-daily for 10–14 days ➢ RECORD4: Oral rivaroxaban 10 mg once-daily for 10–14 days versus subcutaneous enoxaparin 30 mg twice-daily for 10–14 days ➢ 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 (rivaroxaban 6-8 hours and enoxaparin 12-24 hours 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 mid 2008

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

Programme 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	Randomised, open-label, parallel-group, multicentre
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 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

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.

Study design	Randomized, double-blind, parallel-group, multicentre
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

MAGELLAN: VTE prevention in hospitalized, medically ill patients

Multicenter, rAndomized, parallel Group Efficacy superiority study 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 endpoints	Composite of VTE (DVT and/or PE) and Death
Safety endpoints	Individual components of the composite endpoint and other cardiovascular events
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	Randomised, double-blind, parallel-group, multicentre
Patient numbers	> 3,000 patients
Interventions	➢ Rivaroxaban daily doses of 5mg, 10mg, 15mg and 20mg either as OD or BID regimen ➢ 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*	2012

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