About the EINSTEIN Clinical Trial Program

Fast facts

- **The extensive EINSTEIN global clinical development program comprises more than 8,800 patients evaluating oral rivaroxaban in the acute treatment and secondary prevention of venous thromboembolism (VTE)**
- **The EINSTEIN program consists of the three milestone trials EINSTEIN-DVT, EINSTEIN-PE and EINSTEIN-Extension (EXT)**
  - **EINSTEIN-DVT compares rivaroxaban with the combination of injectable enoxaparin followed by a Vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic DVT**
  - **EINSTEIN-PE compares rivaroxaban with the combination of injectable enoxaparin followed by a Vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic PE**
  - **Presented at the 2009 American Society of Hematology meeting, EINSTEIN-EXT compares rivaroxaban to placebo in the long-term prevention of recurrent symptomatic VTE in patients who previously completed 6 or 12 months of anticoagulation treatment**

A major global initiative and innovative study design

EINSTEIN is a global program of three trials in around 8,800 patients evaluating oral rivaroxaban. Two trials, EINSTEIN-DVT and EINSTEIN-PE compare rivaroxaban with enoxaparin in patients with acute DVT and with acute PE.

The EINSTEIN-EXT study was designed to evaluate the benefits of once-daily oral rivaroxaban for the secondary prevention of recurrent VTE versus placebo.

Design of Studies

EINSTEIN-DVT	
Study design	◆ Randomized, open-label, assessor-blind, event-driven, non-inferiority program
Interventions	◆ Oral, twice-daily rivaroxaban 15 mg for three weeks, followed by oral once-daily rivaroxaban 20 mg (single drug approach) ◆ Subcutenaous, twice daily enoxaparin (body weight adjusted) for at least 5 days in combination with VKA until target INR of 2.5 is reached (then LMWH stopped)
Number of patients	◆ 3,400 patients with acute symptomatic DVT without symptomatic PE[1]
Primary efficacy endpoint	◆ Symptomatic recurrent VTE - the composite of recurrent DVT or fatal or non-fatal PE
Primary efficacy analysis	◆ Time to first symptomatic recurrent VTE event
Primary safety endpoint	◆ Major and non-major clinically relevant bleeding*

EINSTEIN-PE	
Study design	◆ Multicenter, randomized, open-label, assessor-blind, event-driven, non-inferiority program ◆ Dose confirmation phase with 400 PE patients ◆ Pre-defined study duration of 3, 6, or 12 months
Interventions	◆ Oral, twice-daily rivaroxaban 15 mg for three weeks, followed by oral once-daily rivaroxaban 20 mg ◆ Subcutenaous, twice daily enoxaparin (body weight adjusted) for at least 5 days in combination with VKA until target INR of 2.5 is reached (then LMWH stopped)
Number of patients	◆ 3,300 patients with acute symptomatic PE with or without symptomatic DVT[2]
Primary efficacy endpoint	◆ Symptomatic, recurrent VTE - the composite of recurrent DVT or fatal or non-fatal PE
Primary efficacy analysis	◆ Time to first symptomatic recurrent VTE event
Primary safety endpoint	◆ Major and non-major clinically relevant bleeding*

EINSTEIN-Extension (EXT)	
Study design	◆ Multi-center, randomized, double-blind, placebo-controlled event-driven, superiority program ◆ Pre-defined study duration of 6 or 12 months
Interventions	◆ Oral, once-daily rivaroxaban 20 mg ◆ Once-daily placebo
Number of patients	◆ 1,147 patients with acute symptomatic DVT or PE who have previously completed 6 or 12 months of treatment with rivaroxaban or VKA[3]
Primary efficacy endpoint	◆ Symptomatic recurrent VTE - the composite of recurrent DVT or fatal or non-fatal PE
Primary efficacy analysis	◆ Time to first symptomatic recurrent VTE event
Primary safety endpoint	◆ Major bleeding*

* Major bleeding is defined as overt bleeding associated with: a fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or bleeding that occurs in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or contributing to death.
Clinically relevant non-major bleeding was defined as bleeding not meeting the criteria for major bleeding but is associated with medical intervention.

References

1 Clinicaltrials.gov, http://clinicaltrials.gov/ct2/show/NCT00440193?term=EINSTEIN+DVT&rank=1
2 Clincialtrials.gov, http://clinicaltrials.gov/ct2/show/NCT00439777?term=EINSTEIN+PE&rank=1
3 Clinicaltrials.gov, http://clinicaltrials.gov/ct2/show/NCT00439725?term=EINSTEIN&rank=1

About Rivaroxaban

Rivaroxaban is a novel oral anticoagulant that was invented in Bayer Schering Pharma's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. In clinical studies, rivaroxaban has been shown to be effective in preventing VTE in adult patients following elective hip or knee replacement surgery. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for coagulation monitoring, as well as a limited potential for food and drug interactions. Rivaroxaban is marketed under the brand name Xarelto® for VTE prevention in adult patients following elective hip or knee replacement surgery, and it is the only new oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin for this indication. Xarelto® is approved in more than 100 countries worldwide and has been successfully launched in more than 75 countries by Bayer Schering Pharma achieving the market leader position among the new oral anticoagulants.

The extensive clinical trial program supporting rivaroxaban makes it the most studied oral, direct Factor Xa inhibitor in the world today. More than 65,000 patients are expected to be enrolled into the rivaroxaban clinical development program, which will evaluate the product in the prevention and treatment of a broad range of acute and chronic blood-clotting disorders, including stroke prevention in patients with atrial fibrillation, secondary prevention of acute coronary syndrome, and VTE prevention in hospitalized, medically ill patients.

To learn more about thrombosis please visit www.thrombosisadviser.com

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