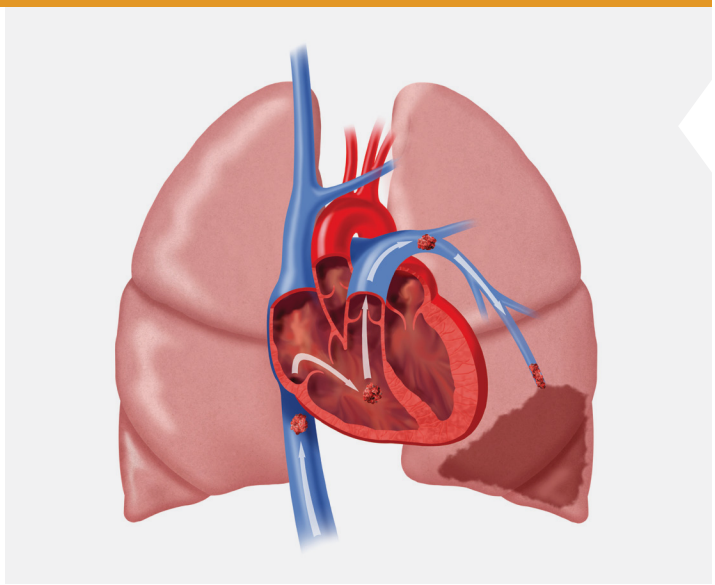
EINSTEIN

A major global initiative and innovative study design



EINSTEIN is a global program of three Phase 3 clinical trials in more than 9,400 patients evaluating the safety and efficacy of rivaroxaban in the prevention of a recurrent, symptomatic venous thromboembolism (also known as venous blood clot or VTE) in patients with acute symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE).

EINSTEIN-DVT compared rivaroxaban to enoxaparin/vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic DVT without symptomatic PE. Results were presented at the 2010 European Society of Cardiology Congress in Stockholm, Sweden (http://www.janssenrnd.com/sites/default/files/pdf/EINSTEIN-DVT_press_release_ESC_2010.pdf#zoom=125).

EINSTEIN-Extension compared the safety and efficacy of rivaroxaban to placebo in the secondary prevention of recurrent symptomatic venous blood clots by prolonging preventative treatment by six or 12 months beyond a previously completed regimen of six or 12 months of therapy. Results were presented at the 2009 Annual Meeting of the American Society of Hematology in New Orleans, Louisiana (http://www.nejm.org/doi/full/10.1056/NEJMoa1007903#t=article).

EINSTEIN-PE compared rivaroxaban to enoxaparin/VKA in the treatment of patients with acute symptomatic PE with or without symptomatic DVT. Results were presented at the 2012 American College of Cardiology Scientific Sessions in Chicago, Illinois.

FAST FACTS

1 VTE can take the form of either:

- DVT, a blood clot in a deep vein (usually in the leg) that partially or totally blocks the flow of blood which may lead to;
- PE, a blood clot in the lungs that can partially or totally block the flow of blood.

2 EINSTEIN is a global program of three Phase 3 clinical trials evaluating the safety and efficacy of rivaroxaban in the treatment and/or prevention of a recurrent, symptomatic VTE in patients with acute symptomatic DVT or PE in almost 9,400 patients.

3 Janssen Research & Development, LLC and Bayer HealthCare are developing rivaroxaban jointly.

The EINSTEIN Studies:

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 rivaroxaban 20 mg once-daily • Subcutaneous, twice-daily enoxaparin 1mg/kg BID for at least 5 days in combination with VKA; VKA continued and enoxaparin discontinued when international normalized ratio (INR) ≥ 2 on two consecutive measurements at least 24 hours apart
Number of patients	4,833 patients with acute symptomatic PE with or without symptomatic DVT
Primary efficacy endpoint	Symptomatic recurrent VTE, i.e., the composite of (recurrent) DVT or fatal or nonfatal PE
Primary efficacy analysis	Time to first symptomatic recurrent VTE event
Safety endpoints	Major * and clinically relevant nonmajor** bleeding
RESULTS:	Presented at the 2012 61st annual American College of Cardiology (ACC) Scientific Session in Chicago, Illinois

For additional information visit **www.clinicaltrials.gov** Identifier: NCT00439777

EINSTEIN-DVT	
Study design	• Multinational, randomized, open-label, assessor-blind, event-driven, non-inferiority program • Pre-defined study duration of 3, 6, or 12 months
Interventions	• Oral, twice-daily rivaroxaban 15 mg for three weeks, followed by oral rivaroxaban 20 mg once-daily • Subcutaneous, enoxaparin 1mg/kg BID for at least 5 days in combination with VKA; VKA continued and enoxaparin discontinued when INR ≥ 2 on two consecutive measurements at least 24 hours apart
Number of patients	3,449 patients with acute symptomatic DVT without symptomatic PE
Primary efficacy endpoint	Symptomatic, recurrent VTE—the composite of recurrent DVT or fatal or nonfatal PE
Primary efficacy analysis	Time to first symptomatic recurrent VTE event
Safety endpoints	Major *and clinically relevant nonmajor** bleeding
RESULTS:	Presented at the 2010 European Society of Cardiology (ESC) Congress in Stockholm, Sweden (http://www.nejm.org/doi/full/10.1056/NEJMoa1007903#t=article)

For additional information visit **www.clinicaltrials.gov** Identifier: NCT00440193

* 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 nonmajor bleeding was defined as bleeding not meeting the criteria for major bleeding but associated with medical intervention

EINSTEIN-EXT	
Study design	• Multicenter, 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 • Placebo once-daily
Number of patients	• 1,197 patients with acute symptomatic DVT or PE who have previously completed 6 or 12 months of treatment with rivaroxaban or VKA • Patients who participated in the ongoing EINSTEIN-DVT or EINSTEIN-PE trials in which patients would have been treated with either rivaroxaban or VKA for 6 or 12 months and patients treated outside that program with VKA for 6 or 12 months following the initial diagnosis of PE or DVT and continued up to the moment of randomization were eligible for enrollment
Primary efficacy endpoint	Symptomatic, recurrent VTE—the composite of recurrent DVT or fatal or nonfatal PE
Primary efficacy analysis	Time to first symptomatic recurrent VTE event
Safety endpoints	Primary: Major bleeding* Secondary: Major plus clinically relevant nonmajor bleeding**
RESULTS:	Presented at the 2009 51st Annual Meeting of the American Society of Hematology (ASH) in New Orleans, Louisiana (http://www.nejm.org/doi/full/10.1056/NEJMoa1007903#t=article)

For additional information visit **www.clinicaltrials.gov** Identifier: NCT00439725

* 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 nonmajor bleeding was defined as bleeding not meeting the criteria for major bleeding but associated with medical intervention