

The EINSTEIN Clinical Trial Programme

What is the EINSTEIN Clinical Trial Programme?

- ◆ The EINSTEIN Programme has been designed to investigate the clinical utility of Xarelto® (rivaroxaban) in the treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and the prevention of recurrent DVT and PE
- ◆ EINSTEIN comprises three clinical studies involving more than 9,000 patients in total: EINSTEIN-DVT, EINSTEIN-PE and EINSTEIN-Extension (EINSTEIN-EXT)
- ◆ **EINSTEIN-DVT** compared 'Xarelto' with the dual drug approach of injectable enoxaparin followed by a Vitamin K antagonist (VKA) in the treatment of patients with acute symptomatic DVT
- ◆ **EINSTEIN-PE** compares 'Xarelto' with the dual drug approach of injectable enoxaparin followed by a VKA in the treatment of patients with acute symptomatic PE
- ◆ **EINSTEIN-EXT** compared 'Xarelto' to placebo in the long-term prevention of recurrent symptomatic venous thromboembolism (VTE) in patients who previously completed 6 or 12 months of anticoagulation treatment
- ◆ **EINSTEIN-DVT and -EXT have completed. EINSTEIN-PE is ongoing**

EINSTEIN Results: Summary

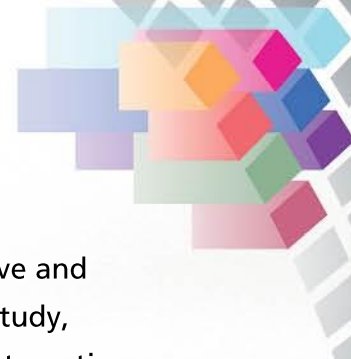
EINSTEIN-DVT

- ◆ EINSTEIN-DVT investigated a unique single-drug approach for the treatment of DVT. In EINSTEIN-DVT, the simple single-drug solution with 'Xarelto' was effective and demonstrated a favourable safety profile compared to the standard of care
- ◆ In EINSTEIN-DVT, 'Xarelto' delivered a significantly improved net clinical benefit (a pre-specified outcome defined as the composite of the primary efficacy outcome plus major bleeding), compared to standard therapy (2.9% vs. 4.2%, respectively), as well as a numerically lower rate of major bleeds¹
- ◆ Additionally, 'Xarelto' was well tolerated, regardless of age, gender and body weight¹
- ◆ Results from EINSTEIN-DVT were published in the New England Journal of Medicine (NEJM)¹

EINSTEIN-PE

- ◆ EINSTEIN-PE is the largest PE trial of all new oral anticoagulants, with data expected in late 2011 or early 2012





EINSTEIN-EXT

- ◆ EINSTEIN-EXT was designed to test an important hypothesis – is ‘Xarelto’ effective and well-tolerated in the long-term secondary prevention of recurrent VTE? In this study, ‘Xarelto’ demonstrated an 82% relative risk reduction in the recurrence of symptomatic VTE compared to placebo - an outcome that was highly statistically significant - with low rates of major bleeding¹
- ◆ Additionally, ‘Xarelto’ was well tolerated, regardless of age, gender and body weight¹
- ◆ Results from EINSTEIN-EXT were published in the New England Journal of Medicine (NEJM)¹

EINSTEIN: Study Design and Results

EINSTEIN-DVT¹	
Study design	◆ Multicentre, randomised, open-label, assessor-blind, event-driven, non-inferiority study
Interventions	<ul style="list-style-type: none"> ◆ Oral, twice-daily ‘Xarelto’ 15 mg for three weeks, followed by oral once-daily ‘Xarelto’ 20 mg (single-drug solution) ◆ Subcutaneous, twice-daily enoxaparin (body weight adjusted) for at least 5 days in combination with VKA until target INR of 2.5 is reached [then low molecular weight heparin (LMWH) stopped]
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 non-fatal PE
Primary efficacy analysis	◆ Time to first symptomatic recurrent VTE event
Secondary efficacy endpoint	◆ Net clinical benefit – the composite of the primary efficacy outcome or major bleeding
Primary safety endpoints	◆ Clinically relevant bleeding – the composite of major or clinically relevant non-major bleeding
RESULTS¹	
Primary efficacy endpoint	◆ ‘Xarelto’ demonstrated non-inferiority in patients with acute symptomatic recurrent DVT compared with the current standard of care of enoxaparin followed by VKA [2.1% vs. 3.0% respectively (p<0.0001 for non-inferiority)]
Secondary efficacy endpoint	◆ Net clinical benefit occurred in 51 (2.9%) of the patients who received ‘Xarelto’ and in 73 (4.2%) of the patients who received standard therapy (hazard ratio, 0.67; 95% CI, 0.47 to 0.95; P = 0.03)
Primary safety endpoint	◆ Similar bleeding compared to the standard of care [8.1% in both treatment groups (p=0.77)]





EINSTEIN-PE²	
Study design	<ul style="list-style-type: none"> ◆ Multicentre, randomised, open-label, assessor-blind, event-driven, non-inferiority study ◆ Pre-defined study duration of 3, 6, or 12 months
Interventions	<ul style="list-style-type: none"> ◆ Oral, twice-daily 'Xarelto' 15 mg for three weeks, followed by oral once-daily 'Xarelto' 20 mg ◆ Subcutaneous, 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	◆ 4,833 patients with acute symptomatic PE with or without symptomatic DVT
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	◆ Clinically relevant bleeding – the composite of major or clinically relevant non-major bleeding*

EINSTEIN-EXT¹	
Study design	<ul style="list-style-type: none"> ◆ Multicentre, randomised, double-blind, placebo-controlled, event-driven, superiority study ◆ Pre-defined study duration of 6 or 12 months
Interventions	<ul style="list-style-type: none"> ◆ Oral, once-daily 'Xarelto' 20 mg ◆ Once-daily placebo
Number of patients	◆ 1,197 patients with acute symptomatic DVT or PE who have previously completed 6 to 12 months of treatment with 'Xarelto' or VKA
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 endpoints	◆ Major bleeding
RESULTS¹	
Primary efficacy endpoint	◆ 82% relative risk reduction (RRR) in the recurrence of symptomatic VTE
Primary safety endpoint	◆ Low rates of major bleeding and not statistically significantly different (p=0.11) between the two groups [0.7% (n=4) vs. 0.0% (n=0), for the 'Xarelto' and placebo arms, respectively]

* Major bleeding is defined as overt bleeding associated with: a fall in haemoglobin 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) Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N.Engl.J.Med.* 2010;363,(26)2499-2510
- 2) Clinicaltrials.gov. Available at <http://clinicaltrials.gov/ct2/show/NCT00439777?term=EINSTEIN+PE&rank=1>. Last accessed November 2011

About Rivaroxaban (Xarelto®)

Rivaroxaban is an oral anticoagulant that was discovered in Bayer HealthCare's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. It has a rapid onset of action with a predictable dose response and high bioavailability, no requirement for routine coagulation monitoring, and 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 oral anticoagulant that has consistently demonstrated superior efficacy over enoxaparin in this indication. Rivaroxaban is approved in more than 110 countries worldwide and marketed outside the U.S. by Bayer HealthCare in this indication.

In the U.S., where rivaroxaban has been available since July 2011 for VTE prevention in adult patients following elective hip or knee replacement surgery, Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company) holds marketing rights. The Bayer HealthCare sales force is supporting Janssen Pharmaceuticals, Inc. in designated hospital accounts. On November 4, Xarelto® received further marketing approval in the U.S. for the prevention of stroke in patients with Atrial Fibrillation.

The extensive clinical trial programme supporting rivaroxaban makes it the most studied and widely published oral, direct Factor Xa inhibitor. The studies, reported and ongoing, involve over 75,000 patients for the prevention and treatment of venous and arterial thromboembolic (VAT) disorders across a broad range of acute and chronic conditions, including stroke prevention in patients with Atrial Fibrillation, DVT treatment and the prevention of recurrent DVT or PE, and the secondary prevention of Acute Coronary Syndrome.

To learn more about thrombosis, please visit www.thrombosisadviser.com
To learn more about 'Xarelto' please visit www.xarelto.com

Media Backgrounder
For Ex-US and Ex-UK Use Only



RIVAROXABAN