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 Phase III clinical studies involving 9,479 patients in total:
  • **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, and the secondary prevention of venous thromboembolism (VTE)
  • **EINSTEIN-PE** compared ‘Xarelto’ with the dual-drug approach of injectable enoxaparin followed by a VKA in the treatment of patients with acute symptomatic PE, and the secondary prevention of VTE
  • **EINSTEIN Extension (EINSTEIN-EXT)** compared ‘Xarelto’ to placebo in the long-term prevention of recurrent symptomatic VTE in patients who previously completed 6 or 12 months of anticoagulation treatment

**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 (p=0.03)], 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 in December 2010
**EINSTEIN-PE**

- EINSTEIN-PE, the largest PE trial of all novel oral anticoagulants, investigated a unique single-drug approach for the treatment of acute PE and the secondary prevention of VTE. In EINSTEIN-PE, the simple single-drug solution with ‘Xarelto’ was as effective as the standard of care and demonstrated a similar safety profile.
- Importantly, patients receiving ‘Xarelto’ experienced half as many major bleeding events compared to patients receiving the standard of care [1.1% vs. 2.2%, respectively (p=0.003)]
- Additionally, low rates of CV events – including acute coronary events, cerebrovascular events and systemic embolism – were observed in EINSTEIN-PE, which was consistent with the standard of care.
- In EINSTEIN-PE, ‘Xarelto’ also showed consistent efficacy and safety, regardless of age, gender, body weight and kidney function.
- Results from EINSTEIN-PE were published in the New England Journal of Medicine (NEJM) in March 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 and similar rates of major bleeding.
- Additionally, ‘Xarelto’ was well tolerated, regardless of age, gender and body weight.
- Results from EINSTEIN-EXT were published in the New England Journal of Medicine (NEJM) in December 2010.
# EINSTEIN: Study Design and Results

## EINSTEIN-DVT

### Study design
- Multicentre, randomised, open-label, assessor-blind, event-driven, non-inferiority study
- Pre-defined treatment duration of 3, 6 or 12 months

### Interventions
- 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

## RESULTS

### 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<0.001 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** | ♦ Multicentre, randomised, open-label, assessor-blind, event-driven, non-inferiority study  
  ♦ Pre-defined treatment duration of 3, 6 or 12 months |
|------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Interventions** | ♦ 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 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 and clinically relevant non-major bleeding* |

### RESULTS²

| **Primary efficacy endpoint** | ♦ ‘Xarelto’ demonstrated non-inferiority in patients with acute symptomatic PE compared with the current standard of care of enoxaparin followed by VKA [2.1% vs. 1.8% respectively (p=0.003 for non-inferiority)] |
| **Primary safety endpoint** | ♦ ‘Xarelto’ demonstrated similar overall bleeding rates [10.3% vs. 11.4%, respectively (p=0.23)]  
  ♦ Furthermore, ‘Xarelto’ was associated with significantly lower rates of major bleeding events vs. the current standard of care [1.1% vs. 2.2% (p=0.003), respectively] |
**EINSTEIN-EXT**

| Study design | ♦ Multicentre, randomised, double-blind, placebo-controlled, event-driven, superiority study  
♦ Pre-defined treatment duration of 6 or 12 months |
| Interventions | ♦ 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 |

**RESULTS**

| 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, unscheduled physician contact, temporary cessation of study treatment, or discomfort such as pain or impairment of activities of daily life.

**References**


About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, Xarelto has been approved for use in the following venous arterial thromboembolic (VAT) indications:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors in more than 70 countries worldwide
- The treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults in more than 70 countries worldwide
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery in more than 120 countries worldwide

Since the first approval of Xarelto in 2008 in the orthopaedic setting, more than two and a half million patients worldwide have received Xarelto in daily clinical practice in this indication alone.

Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a Xarelto Patient Card for patients to support best practices. To learn more, please visit: https://prescribe.xarelto.com.

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