EINSTEIN

The EINSTEIN Clinical Development Programme has been Designed to Investigate the Clinical Utility of Rivaroxaban in the Treatment and Prevention of Recurrent Venous Thromboembolism (VTE)

Three Pivotal Studies Involving >9,000 Patients Completed

Two Ongoing Studies

Exploring Rivaroxaban in Treatment and Prevention of Recurrent VTE

The completed EINSTEIN Studies examined 'Xarelto' as an oral, single-drug treatment that consists of an intensified treatment of 15 mg twice daily for 21 days, followed by once-daily 20 mg dose to ensure efficient protection in both the acute and long-term phases.

COMPLETE

EINSTEIN DVT

- Proved the oral, single-drug treatment with 'Xarelto' is effective and well-tolerated in treating patients with deep vein thrombosis (DVT), and provides simplified treatment management from hospital to home without the need for injections or routine coagulation monitoring[1]

EINSTEIN PE

- The only dedicated pulmonary embolism (PE) trial of any novel oral anticoagulant (OAC), proved the oral, single-drug treatment with 'Xarelto' is effective and well-tolerated in protecting against the life-threatening risk of PE without the need for injections or routine coagulation monitoring[2]

EINSTEIN DVT

- Demonstrated that oral, once-daily 'Xarelto' is effective and well-tolerated in lowering the risk of recurrent symptomatic VTE[1]

ONGOING

EINSTEIN CHOICE

- Will assess different doses of oral, once-daily rivaroxaban in comparison to acetylsalicylic acid for the long-term, secondary prevention of symptomatic VTE in approximately 2,850 patients

EINSTEIN JUNIOR

- Will investigate rivaroxaban according to an age- and body weight-adjusted dosing schedule for the treatment and secondary prevention of VTE in approximately 150 paediatric patients

The extensive evaluation of rivaroxaban to protect different patient populations at risk of venous and arterial thromboembolism (VAT), makes it the most studied novel oral anticoagulant in the world. Rivaroxaban (Xarelto®) is already approved for five indications in seven areas of use and its investigation - both completed and ongoing - will include more than 275,000 patients in clinical trials and real world settings.

Study	Publication	Date
EINSTEIN DVT and EINSTEIN EXT	New England Journal of Medicine[1]	December 2010
EINSTEIN PE	New England Journal of Medicine[2]	March 2012
EINSTEIN DVT and EINSTEIN PE	Thrombosis Journal[3]	September 2013

These three studies were the basis of the approval of 'Xarelto' for the treatment and prevention of DVT and PE in adult patients in more than 105 countries worldwide.

Completed Study Results EINSTEIN DVT PE EXT

EINSTEIN DVT

- The oral, single-drug treatment with 'Xarelto' was effective in treating patients with DVT and demonstrated a favourable safety profile compared to the dual-drug treatment with low molecular weight heparin (LMWH) and vitamin K antagonist (VKA)[1]
- 'Xarelto' delivered a significantly improved net clinical benefit, compared to dual-drug therapy (2.9% vs. 4.2%; p-value 0.03), as well as a numerically lower rate of major bleeds[1]
- 'Xarelto' was well-tolerated, regardless of age, gender and body weight[1]

EINSTEIN PE

- The oral, single-drug treatment with 'Xarelto' was as effective as the dual-drug treatment and demonstrated a similar safety profile[2]
- Major bleeding rates were halved in patients receiving 'Xarelto' compared to patients receiving the dual-drug treatment (1.1% vs. 2.2%; p-value 0.003)[2]
- Similar low rates of cardiovascular events – including acute coronary events, cerebrovascular events, systemic embolism – were observed with 'Xarelto' compared to dual-drug therapy[2]
- Benefits of 'Xarelto' were consistent regardless of age, gender, body weight and kidney function[2]

EINSTEIN DVT and EINSTEIN PE Pooled (>8,000 patients)

- Effectiveness of the oral, single-drug treatment with 'Xarelto' compared to dual-drug therapy was confirmed in pooled data (HR 0.89 (95% CI 0.66-1.19)), with similar overall major or non-major clinically relevant bleeding rates (HR 0.93 (95% CI 0.81-1.06))[3]
- 'Xarelto' was associated with 46% (p-value 0.002) fewer major bleeding events, including fatal bleeding, compared to dual-drug therapy[3]
- Overall, the principal efficacy and safety results of 'Xarelto' were similar compared with standard-therapy, regardless of age, gender, body weight, frailty or renal function[3]

EINSTEIN Extension (EINSTEIN-EXT)

- Oral, once-daily 'Xarelto' demonstrated an 82% relative risk reduction in the recurrence of symptomatic VTE compared to placebo[1]
- 'Xarelto' was well-tolerated, regardless of age, gender and body weight[1]

Fast Facts on Venous Blood Clots

- **Blood clots obstructing blood flow in deep veins or in the lungs kill one person every 37 seconds in the western world[4]**
- **10-25% of PEs are rapidly fatal[5,6], usually within two hours of the onset of symptoms[7]**
- **DVT and PE require urgent action to save lives**
- **The drawbacks of LMWHs and VKAs challenge optimal patient treatment**

References

1) Bauersachs R, Scott D, Berkowitz MD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N.Engl.J.Med. 2010; 363, (26) 2499-2510. **2)** Buller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N.Engl.J.Med. 2012; 366, (14)1287-1297. **3)** Prins MH, Lensing AWA, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thrombosis Journal 2013, 11:21. **4)** Thrombosis Research Institute. About Venous Thromoboembolism. Available at: http://www.tri-london.ac.uk/garfield-vte/information/about-vte. Accessed January 2015. **5)** Kearon C. Natural history of venous thromboembolism. Circulation. 2003; 107, (23 Suppl 1) I22-I30. **6)** Heit JA. The epidemiology of venous thromboembolism in the community: Implications for prevention and management. J Thromb Thrombolysis. 2006; 21,(1) 23-29. **7)** Anderson F, Audet AM. Preventing Deep Vein Thrombosis and Pulmonary Embolism: A Practical Guide to Evaluation and Improvement. Center for Outcomes Research. Anderson F, Audet AM. Umass Medical School. 1998. Available at: http://www.outcomes-umassmed.org/DVT/best_practice/. Accessed January 2015.