The ROCKET AF Study

What is the ROCKET AF Study?

- ROCKET AF (**R**ivaroxaban **O**nce-daily oral direct Factor Xa inhibition **C**ompared with vitamin **K** antagonism for prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation) was a Phase III prospective, randomised, double-blind, double-dummy parallel group outcomes study. It compared once-daily Xarelto® (rivaroxaban) (20 mg, or 15 mg for patients with moderate renal impairment) with dose-adjusted warfarin in 14,264 patients with non-valvular atrial fibrillation (AF) who were at risk for stroke or non-CNS (central nervous system) systemic embolism

- ROCKET AF was an event-driven trial, which ended when the pre-specified number of events was accumulated. The primary objective of ROCKET AF was to demonstrate the efficacy of once-daily 'Xarelto' as non-inferior to dose-adjusted warfarin in the prevention of stroke and non-CNS systemic embolism in patients with non-valvular AF. The principal safety measure of ROCKET AF was the composite of major plus non-major clinically relevant bleeding events

- ROCKET AF studied a population of patients at moderate to high risk of stroke with multiple comorbidities. Patients with multiple comorbidities are typically more difficult to protect from stroke[1]

- ROCKET AF was presented at the American Heart Association (AHA) Congress in 2010 and published in the New England Journal of Medicine (NEJM) in September 2011[2]

ROCKET AF Results Summary

- In the study, fixed-dose, once-daily 'Xarelto' was proven to be as effective as dose-adjusted warfarin in the prevention of stroke and non-CNS systemic embolism in patients with non-valvular AF[2]

- The principal safety outcome – the composite of major and non-major clinically relevant bleeding events – was similar in both treatment arms. Individually, major bleeding was also similar to warfarin. While major bleeding associated with haemoglobin loss and blood transfusion occurred more often in the rivaroxaban group, patients on 'Xarelto' suffered significantly fewer bleeding events of most concern to clinicians, including bleeding into a

critical organ or fatal bleeding. Importantly, patients on 'Xarelto' showed significantly fewer intracranial haemorrhages (ICH) – the most feared bleeds – compared with warfarin[2]

- In ROCKET AF, 'Xarelto' was shown to have a reassuring cardiovascular profile with no increase in myocardial infarctions compared to warfarin[2]

- These results were achieved with a simple one tablet, once-daily, fixed dosing regimen unique to 'Xarelto'[3] (including a reduced fixed 15 mg dose in patients with moderate renal impairment), in patients at risk of stroke and showed consistent results in all patient groups, including those with multiple comorbidities, who are considered more difficult to protect

- A sub-analysis of ROCKET AF investigated the efficacy and safety of 'Xarelto' compared with warfarin among patients with and without previous stroke or transient ischaemic attack (TIA). This sub-analysis demonstrated consistent safety and efficacy among the patient subgroups and supports the use of 'Xarelto' as an alternative to warfarin for both primary and secondary stroke prevention in patients with AF. These results, which were consistent with those seen in the overall ROCKET AF study, were published in The Lancet Neurology in March 2012[4]

- An additional ROCKET AF sub-analyses of 2,950 patients with non-valvular AF and moderate renal impairment was published in the European Heart Journal in August 2011 and demonstrated that 'Xarelto' can prevent stroke in patients with moderate renal insufficiency, without elevating the risk of critical bleeding events such as ICH. Patients with moderate renal impairment are at increased risk for ischaemic stroke and bleeding during anticoagulation. This sub-analysis showed consistent results for 'Xarelto' across dosing groups for both renally impaired patients (15 mg) and patients without renal impairment (20 mg). Additionally, dose adjustment in ROCKET AF yielded efficacy and safety results consistent with the overall study in comparison with dose-adjusted warfarin[5]

- Findings from a further ROCKET AF sub-analysis of 6,229 patients with non-valvular AF over the age of 75 were presented at the International Stroke Conference (ISC) 2012. AF patients over the age of 75 are at higher risk of stroke and severe bleeding than younger patients, and are considered to be a patient population more difficult to manage. The sub-analysis of this higher risk group showed consistent efficacy and safety benefits by comparison to warfarin, reflecting the overall ROCKET AF findings. Importantly, elderly patients treated with 'Xarelto' showed lower rates of intracranial bleeding compared to patients receiving warfarin, which was also consistent with ROCKET AF results[6]

- A second sub-analysis of 136 patients was presented at ISC 2012, which identified risk factors for intracranial bleeding among AF patients in ROCKET AF. The average annual rate of ICH observed in these patients was 0.55% per year and was influenced by a number of independent risk factors, including prior stroke or TIA, high diastolic blood pressure and low platelet count. Importantly, patients treated with 'Xarelto' were associated with a significantly lower risk of ICH than patients treated with warfarin[7]

ROCKET AF: Rivaroxaban Once-Daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for the prevention of stroke and Embolism Trial in Atrial Fibrillation[2]	
Study design	♦ Randomised, double-blind, event-driven trial (more than 1,100 centres across 45 countries worldwide with a 2-year median follow-up)
Interventions	♦ Oral, one-tablet, once-daily 'Xarelto' 20 mg (15 mg once daily for patients with moderate renal impairment at screening) ♦ Warfarin once daily titrated to an International Normalised Ratio of 2-3
Number of patients	♦ 14,264
Study inclusion criteria	♦ Documented non-valvular AF ♦ Prior stroke, or transient ischaemic attack (TIA), or systemic embolism or at least 2 of the following: Congestive heart failure LVEF ≤35%, hypertension, age ≥75 years, diabetes mellitus
Primary efficacy endpoint	♦ Composite of stroke and non-CNS systemic embolism (blood clots occluding vessels outside the brain)
Primary safety endpoint	♦ Composite of major and non-major clinically relevant bleeding events
Safety endpoints	♦ Major bleeding/non-major clinically relevant bleeding
RESULTS[2]	
Primary efficacy endpoint	♦ 'Xarelto' was shown to be non-inferior to warfarin
Primary safety endpoint	♦ Overall bleeding rates were comparable to warfarin ♦ 'Xarelto' demonstrated a reassuring bleeding profile: similar overall bleeding rates with a significant reduction in intracranial haemorrhages and fatal bleeds
TRIAL ATTRIBUTES	
Patients eligible for anticoagulation according guidelines	♦ Patients recruited were at moderate to high risk for stroke and recommended anticoagulation therapy with warfarin according to current guidelines
Primary and secondary prevention of stroke	♦ Approximately half of patients included in the study had a history of stroke, transient ischaemic attack (TIA), or systemic embolism ♦ Therefore, the ROCKET AF trial population allowed for the assessment of the clinical benefit of 'Xarelto' for both primary and secondary prevention of stroke in AF patients
Age	♦ AF is more prevalent among the elderly; this age group is frequently under-treated with current therapies and often under-represented

	in clinical trials. The ROCKET AF study population had a higher mean age than other trials in this disease area (average 73.1 years). A quarter of patients were 78 years or older

References

1) Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285,(22)2864-2870
2) Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365(10):883-891
3) Xarelto [summary of product characteristics]. Berlin, Germany: Bayer Pharma AG; \May 2012
4) Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol.* 2012; [Epub ahead of print]
5) Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J.* 2011;32(19): 2387–2394
6) Halperin JL, Wojdyla D, Piccini JP, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the ROCKET-AF trial. *Stroke.* 2012;43: A148, Abstract only. Available at http://stroke.ahajournals.org/cgi/content/meeting_abstract/43/2_MeetingAbstracts/A148?sid=a1f93b83-b0c7-4622-8470-685545bed757 Last accessed March 2012
7) Hankey GJ, Stevens S, Piccini JP, et al. Predictors of intracranial hemorrhage among anticoagulated patients with atrial fibrillation: Insights from the rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Stroke.* 2012;43: A152, Abstract only. Available at http://stroke.ahajournals.org/cgi/content/meeting_abstract/43/2_MeetingAbstracts/A152?sid=a1f93b83-b0c7-4622-8470-685545bed757 Last accessed March 2012

About Xarelto® (Rivaroxaban)

Rivaroxaban is the most broadly indicated novel oral anticoagulant and is marketed under the brand name Xarelto®. To date, 'Xarelto' is approved for five indications across seven distinct areas of use, consistently protecting patients across more venous and arterial thromboembolic (VAT) conditions than any other novel OAC:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors
- The treatment of deep vein thrombosis (DVT) in adults
- The treatment of pulmonary embolism (PE) in adults
- The prevention of recurrent DVT and PE in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective knee replacement surgery
- The prevention of atherothrombotic events (cardiovascular death, myocardial infarction or stroke) after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine)

Whilst licences may differ from country to country, across all indications 'Xarelto' is approved in more than 120 countries.

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