

Rationale and design of the ROCKET AF study: Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

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Introduction

- ◆ Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia of clinical significance¹
 - It predisposes patients to the development of atrial thrombi, and significantly increases the risk of stroke; up to 15% of all strokes, and 36% of strokes in those aged over 80 years, are attributable to AF²
- ◆ Currently, the vitamin K antagonist (VKA) warfarin is the most effective therapy for AF patients, as it has been shown to significantly reduce the risk of stroke¹
 - Its use, however, is associated with several limitations, particularly the need for frequent monitoring to maintain coagulation within the target international normalized ratio (INR) range (2.0–3.0)
- ◆ Rivaroxaban is an oral, direct Factor Xa inhibitor approved in the EU for the prevention of venous thromboembolism in adult patients after total hip or knee replacement surgery, following the completion of the large phase III RECORD programme.^{3–6} It is also in advanced development for the prevention and treatment of other thromboembolic disorders

Objective

- ◆ To present the rationale for, and design of, a large international phase III study evaluating rivaroxaban compared with dose-adjusted warfarin for the prevention of thromboembolic events in patients with non-valvular AF

Methods

Study design

- ◆ ROCKET AF (Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) is a phase III, prospective, randomized, double-blind, double-dummy, active-controlled, multi-centre, event-driven study

- ◆ The study is divided into a screening period, a double-blind period, and an observation period. At the end of the double-blind period, patients are transitioned from the study drug to appropriate open-label therapy (Figure 1)
- ◆ Inclusion criteria: persistent or paroxysmal AF documented on at least two episodes and a history of stroke; transient ischaemic attack or non-central nervous system (CNS) systemic embolism; or two or more of the following risk factors: age ≥75 years; hypertension; a clinical diagnosis of heart failure and/or left ventricular ejection fraction ≤35%; or diabetes mellitus
- ◆ Exclusion criteria include: patients with AF and valvular disease (such patients were not included in previous placebo-controlled studies of warfarin therapy); transient AF caused by a reversible disorder; haemorrhagic risk; and planned cardioversion
- ◆ Patients are seen 1, 2, and 4 weeks after randomization, and every month thereafter

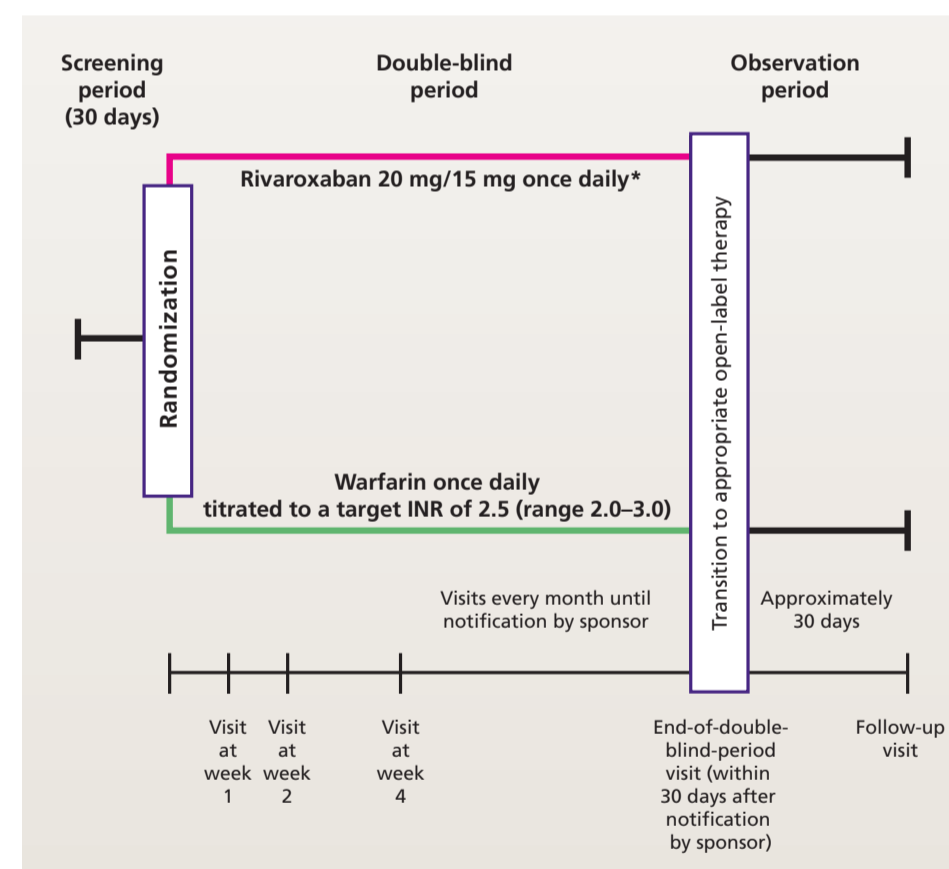


Figure 1. ROCKET AF study flow. *Patients with a calculated creatinine clearance of 30–49 ml/min receive rivaroxaban 15 mg once daily. INR, international normalized ratio.

Intervention

- ◆ Patients are allocated to either one of the following regimens:
 - Rivaroxaban 20 mg once daily (od), or 15 mg od in patients with a creatinine clearance of 30–49 ml/min, plus oral warfarin placebo od titrated to a target sham INR of 2.5 (range 2.0–3.0; Figure 1)
 - Oral warfarin od, titrated to a target INR of 2.5 (range 2.0–3.0), plus oral rivaroxaban placebo od (Figure 1)

- ◆ INR values are provided to investigators through point-of-care INR devices (to maintain blinding), and warfarin and matching rivaroxaban–placebo, or rivaroxaban and matching warfarin–placebo, are dose adjusted based on either true or sham INR results
- ◆ Investigators are encouraged to manage patients with concurrent interventions according to the local standard of care, to ensure that the study reflects current clinical practice

Efficacy evaluation

- ◆ The primary objective of the study is to demonstrate that the efficacy of rivaroxaban is non-inferior to that of dose-adjusted warfarin (INR 2.0–3.0) for the prevention of thromboembolic events in patients with non-valvular AF
- ◆ The primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism
 - This will be analyzed (non-inferiority) in all randomized patients, except those who have major protocol violations prior to having a primary endpoint event (the per-protocol population)
- ◆ Secondary efficacy endpoints include stroke, non-CNS systemic embolism, all-cause death, vascular death, and myocardial infarction

Safety evaluation

- ◆ The principal safety objective is to demonstrate that rivaroxaban is superior to dose-adjusted warfarin, as assessed by the composite of major and clinically relevant non-major bleeding events (the primary safety endpoint)
 - Major bleeding is defined as bleeding associated with any of the following criteria: a fatal outcome; involving a critical site (i.e. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal); or clinically overt (associated with a fall in haemoglobin of ≥2 g/dl, or leading to the transfusion of two or more units of packed red blood cells or whole blood)
 - Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study drug, or bleeding leading to discomfort for the patient
- ◆ Safety analyses will be performed on randomized subjects who take at least one dose of study drug (the safety analysis population)

Statistical analysis

- ◆ The study is powered to show non-inferiority of rivaroxaban to warfarin for the primary efficacy endpoint
- ◆ The test for superiority will only be performed if non-inferiority is demonstrated

Preliminary patient demographics

- ◆ Enrolment is now complete; a total of 14,269 patients have been randomized at over 1,100 sites in 45 countries
 - The median age is 73 years, and approximately 40% of patients are female
- ◆ Approximately 35% of patients were naïve to VKA therapy at the time of randomization
- ◆ Over 90% of patients have hypertension, 63% have heart failure, and 40% have diabetes
- ◆ Over 50% of patients have a history of stroke, transient ischaemic attack, or non-CNS systemic embolism
- ◆ 20% of patients are receiving concomitant acetylsalicylic acid therapy

Conclusions

- ◆ The phase III ROCKET AF study will determine the efficacy and safety of od rivaroxaban – an oral, direct Factor Xa inhibitor – as an alternative to warfarin for the prevention of stroke and non-CNS systemic embolism in patients with AF
- ◆ The first patient was enrolled in December 2006 and enrolment is now complete
- ◆ This event-driven trial will be approximately 40 months in duration

References

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Disclosure of conflict of interest

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