A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation (39039039AFL3001)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON35625

Source
ToetsingOnline

Brief title
ROCKET-AF

Condition

- Cardiac arrhythmias

Synonym
atrial fibrillation, thromboembolic complications

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Johnson & Johnson

Intervention

Keyword: Atrial fibrillation, Prevention, Rivaroxaban, Stroke

Outcome measures

Primary outcome

The primary efficacy outcome is the composite of stroke and non CNS systemic embolism.

Secondary outcome

Major secondary efficacy endpoints include the composite of stroke, non CNS systemic embolism, and vascular death; and the composite of stroke, non CNS systemic embolism, myocardial infarction, and vascular death. Other secondary efficacy endpoints include: individual components of the composite primary and major secondary efficacy endpoints; disabling stroke; and all-cause mortality.

Study description

Background summary

Rivaroxaban is a potent and highly selective oral direct factor Xa (FXa)

inhibitor. Activation of factor X to FXa plays a central role in the cascade of blood coagulation. Therefore, its selective inhibition by rivaroxaban should inhibit thrombin generation and may result in a better efficacy and safety profile than available anticoagulants.

Study objective

The primary objective of this study is to demonstrate that the efficacy of rivaroxaban, a direct FXa inhibitor, is non-inferior to that of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular atrial fibrillation as measured by the composite of stroke and non-central nervous system (non-CNS) systemic embolism.
Hypothesis: Rivaroxaban is non-inferior to warfarin in the prevention of the composite endpoint of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation.
The principal safety objective of this study is to demonstrate that rivaroxaban is superior to dose adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.
The major secondary efficacy objectives are to compare the effects of rivaroxaban and warfarin with respect to the composite of stroke, non-CNS systemic embolism, and vascular death and the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Other secondary efficacy objectives are to compare the effects of rivaroxaban and warfarin with respect to the individual components of the composite primary and major secondary endpoints, disabling stroke (modified Rankin Scale score of 3 to 5 inclusive), and all-cause mortality.
Other safety objectives are to compare rivaroxaban and warfarin with respect to the individual bleeding event categories, adverse events, and clinical laboratory evaluations (including liver function tests [LFTs]).
Exploratory objectives include pharmacokinetic (PK), pharmacodynamic (PD), pharmacogenomic, risk marker/proteomics, treatment satisfaction and health care resource utilization (HCRU) evaluations.

Study design

This is a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter, event-driven study comparing the efficacy and safety of rivaroxaban with warfarin for the prevention of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation. An independent blinded Clinical Enpoint Committee (CEC) will apply the protocol definitions and adjudicate and classify the following endpoints: stroke, non-CNS systemic embolism, death, myocardial infarction, transient ischemic attack (TIA), major bleeding event and non major clinically relevant bleeding event.
The study will be divided into a screening period, a double-blind treatment period closing with an end*of study visit, and a posttreatment observation

period. At the end-of-study visit or at an early study medication discontinuation visit for premature discontinuation of study therapy, subjects will be transitioned from study drug to an open-label vitamin K antagonist (VKA) or other appropriate therapy. At the end of the posttreatment observation period, a follow-up visit will occur. The duration of the treatment period for a given subject will depend on the time required to accrue 405 adjudicated primary efficacy endpoint events, i.e., stroke, non-CNS systemic embolism, in the per protocol population. As a result, the time on study drug will vary from subject to subject depending upon the time of the subject*s enrollment. The expected maximum duration of the study is 32 months, but may extend to a maximum of 4 years depending upon the rate of subject recruitment and endpoint event rates. Approximately 14,000 subjects are expected to enroll in this study. However, the sample size may be increased to a maximum of 16,000 subjects if needed.
Subjects with non valvular atrial fibrillation, who are at risk for stroke and non CNS systemic embolism will be randomized into the study using an Interactive Voice Response System (IVRS). Eligible subjects are those with a prior stroke, TIA or non CNS systemic embolism or who have 2 or more of the following risk factors: age >_75 years, hypertension, heart failure and/or left ventricular ejection fraction <_35% or diabetes mellitus. Once all of the inclusion criteria and none of the exclusion criteria have been met, subjects will be randomly assigned to 1 of 2 treatment groups: rivaroxaban or warfarin. Those subjects assigned to rivaroxaban will receive rivaroxaban 20 mg p.o. once daily plus warfarin placebo p.o. once daily titrated to a target sham International Normalized Ratio (INR) of 2.5 (range 2.0 to 3.0, inclusive). Subjects with moderate renal impairment at screening (defined as calculated creatinine clearance [CLCR] between 30 and 49 mL/min, inclusive) will have a dose adaptation to rivaroxaban 15 mg p.o. once daily. Those subjects assigned to warfarin will receive warfarin p.o. once daily titrated to a target INR of 2.5 (range 2.0 to 3.0, inclusive) plus rivaroxaban placebo p.o. once daily. Sham INRs will be generated according to an algorithm reflecting the distribution of INR values from a population of warfarin-treated subjects similar to the study population, and periodically updated in the IVRS based on the distribution of INR values from study subjects assigned to the warfarin treatment. The sham INRs will be based on real subject data that take previous warfarin doses, age, and sex into account.
To maintain the blind, warfarin and its matching placebo will be dose adjusted based on either real or sham INR results, respectively. To accomplish this, study sites will be provided with a specially designed point-of-care INR device that displays a code number instead of the actual INR value. This code number is entered into the IVRS along with the subject*s study identification number. The IVRS will decode the INR code number and then issue a standardized report containing the actual INR value if the subject is assigned to receive warfarin or a sham value if the subject is assigned to receive rivaroxaban. The INR provided by the IVRS must be used by the investigator to adjust the warfarin/warfarin placebo dose in all subjects from the time of randomization until transition from study drug to an open-label VKA or other appropriate

therapy. While on study drug, unblinded INR measurements must not be performed except in case of a medical emergency. It is especially important to limit site personnel knowledge of any unblinded INR values to a minimum. Furthermore, it is important to always use the point-of-care device provided to measure the INR to ensure consistency of warfarin dosing. In addition, during the study, it is recommended that INR monitoring (using the point-of-care device provided) occur as clinically indicated but at least every 4 weeks.
The screening period will begin up to 30 days before randomization of the subject into the study. At the screening visit, study personnel will explain the nature of the study and obtain informed consent from the subject before the initiation of any study-related procedures. Any adverse events that occur after the signing of the informed consent will be recorded. Once a subject is determined to be eligible for the study, the subject will be instructed to discontinue their VKA (if applicable); in this case, daily unblinded INRs should be performed at the treating institution (i.e., not using the point-of-care device) and randomization of the subject should occur within 36 hours as the INR falls below 3.0. Once the subject*s eligibility for the study has been reconfirmed, the subject will be randomized (Day 1) and study drug will be dispensed. The first dose of study drug will be taken that evening with food. A blood sample will be collected on the day of randomization (Day 1 is preferred, any time after informed consent is obtained is acceptable) from subjects consenting to the optional pharmacogenomic component of the study. Subjects will return for visits at Week 1, 2, 4, and then every 4 weeks thereafter for the duration of the double-blind treatment period. After Week 1, all visits during the first year will be Full Visits. Double blind treatment visits occurring after 1 year will take place every 4 weeks and either a Brief Visit or a Full Visit will be performed according to the Visit Schedule provided in the Time and Events Schedule. A 12-lead electrocardiogram (ECG) and clinical laboratory tests will be performed annually and at the screening visit. The frequency and timing of PK, PD, efficacy, safety, or other measurements are provided in the Time and Events Schedules. All randomized subjects will be followed until the study ends (405 adjudicated endpoint events reached followed by study closure activities) even if they did not take study drug or prematurely discontinued study drug. Every effort will be made to contact any subjects lost to follow up and collect information on the occurrence of efficacy endpoint events and the reason for discontinuation. When the pre-specified number of adjudicated primary efficacy endpoint events has been reached in the per protocol population, the sites will be notified by the sponsor to schedule each subject still receiving blinded study medication for an end-of study visit. This visit should be completed as soon as possible, but within 30 days after site notification. At the end-of-study visit, subjects will be transitioned from blinded study drug to an open label VKA or other appropriate therapy and followed in the posttreatment observation period. The posttreatment observation period ends with a follow-up visit, which will be performed approximately 30 days (+/-5 days) after the end of study visit. Subjects who have previously prematurely discontinued study drug will be contacted for a final assessment of efficacy endpoint events within 30 days of

site notification.
An Executive Committee (EC) will be formed that has overall responsibility for the conduct and reporting of the study. An independent Data Monitoring Committee (DMC) will be commissioned for this study. This committee will monitor the progress of the study and ensure that the safety of subjects is not compromised. Any recommendations from the DMC will be made to the EC. An independent blinded Clinical Endpoint Committee (CEC) will apply the protocol definitions and adjudicate and classify the following endpoints: stroke, non CNS systemic embolism, death, myocardial infarction, TIA, major bleeding event, and non major clinically relevant bleeding event. Adjudicated results will be used for final analyses.
An interim review of efficacy and safety data will be performed when 50% of the primary efficacy events as reported by the investigators have occurred to assess the option of stopping early for futility. All available data will be used for the interim analysis.

Intervention

Subjects will be randomly assigned to 1 of 2 treatment groups: rivaroxaban or warfarin. Subjects assigned to rivaroxaban will receive rivaroxaban 20 mg p.o. once daily plus warfarin placebo p.o. once daily titrated to a target sham INR of 2.5 (range 2.0 to 3.0, inclusive). Subjects with moderate renal impairment at screening (defined as calculated CLCR between 30 and 49 mL/min, inclusive) will have a dose adaptation to rivaroxaban 15 mg p.o. once daily. Those subjects assigned to warfarin will receive warfarin p.o. once daily titrated to a target INR of 2.5 (range 2.0 to 3.0, inclusive) plus rivaroxaban placebo p.o. once daily.

Study burden and risks

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS:
Sparse samples for PD evaluations will be collected in all subjects. The PD measurements will include prothrombin time (PT), FXa activity, and prothrombinase induced clotting time (PiCT). Matched PK and PD samples will be collected at yet to be identified, selected sites that can provide the logistical requirements necessary for rich sampling in a limited number of subjects. Together this data will be used to describe drug exposure and exposure/response relationships.
EFFICACY EVALUATIONS/CRITERIA:
The primary efficacy outcome is the composite of stroke and non CNS systemic embolism. Major secondary efficacy endpoints include the composite of stroke, non CNS systemic embolism, and vascular death; and the composite of stroke, non CNS systemic embolism, myocardial infarction, and vascular death. Other secondary efficacy endpoints include: individual components of the composite primary and major secondary efficacy endpoints; disabling stroke; and all-cause mortality.

SAFETY EVALUATIONS:
The principal safety endpoint is the composite of major and non-major clinically relevant bleeding events. Safety will also be assessed by evaluation of adverse events, including bleeding events, clinical laboratory tests (including LFTs), ECGs, vital signs, and physical examinations.
HEALTH ECONOMIC EVALUATIONS:
The following HCRUs will be assessed: hospitalizations (total days length of stay, ICU/CCU days), emergency room visits, unscheduled outpatient physician consultations or visits related to bleeding, surgeries, other selected procedures (inpatient and outpatient) and post stroke care status.
Anti-Clot Treatment Scale (ACTS): Subject satisfaction with treatment will be measured with the ACTS in a subset of the population from the United States (n=500), Germany (n=300) and Netherlands (n=300). The ACTS questionnaire will be cross-validated against a general treatment satisfaction questionnaire (Treatment Satisfaction Questionnaire for Medication [TSQM] version II) within this subset.
RISK MARKERS/PROTEOMICS:
In a subset of 5,000 subjects at (yet to be identified) select sites, 2 blood samples will be collected for assessment of risk markers (e.g., D dimer) and proteomics.

Contacts

Public
Bayer

51368 Leverkusen
Duitsland
Scientific
Bayer

51368 Leverkusen
Duitsland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Adult subjects with non valvular atrial fibrillation and prior stroke, TIA or non CNS systemic embolism or who have 2 or more of the following risk factors: age >_75 years, hypertension, heart failure and/or left ventricular ejection fraction <_35% or diabetes mellitus.

Exclusion criteria

Patients with cardiac-related conditions, hemorrhage risk-related criteria and concomitant conditions and therapies that will have an impact on the wellbeing of the patient when used simultaneously with the studymedication.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2007
Enrollment:	300

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Coumadin
Generic name:	warfarin
Product type:	Medicine
Brand name:	nog niet geregistreerd voor deze indicatie
Generic name:	rivaroxaban

Ethics review

Approved WMO Date:	09-01-2007
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-02-2007
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	23-04-2007
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	24-07-2007
Application type:	Amendment
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	23-11-2007
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO Date:	24-04-2008
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	10-06-2008
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-01-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	11-05-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	14-05-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	26-11-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-004595-13-NL
ClinicalTrials.gov	NCT00403767
CCMO	NL15793.094.06