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LABORATORY OF BIOMATHEMATICS

M.SC. "RESEARCH METHODOLOGY IN BIOMEDICINE, BIOSTATISTICS AND CLINICAL BIOINFORMATICS

MASTER THESIS

A PHASE 3, ACTIVE (WARFARIN) CONTROLLED, DOUBLE-BLIND, DOUBLE-DUMMY, RANDOMIZED STUDY FOR ASSESSING THE EFFICACY AND SAFETY OF RIVAROXABAN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.

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Abbreviations

AE	Adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CEC	Clinical Endpoint Committee
CHA2DS2-VASc score	a score that calculates the stroke risk for patients with atrial fibrillation
CLCR	creatinine clearance
CNS	central nervous system
CRF	case report form
DMC	Data Monitoring Committee
DVT	deep vein thrombosis
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
ITT	intention-to-treat
IVRS	interactive voice response system
LFT	liver function test
LMWH	low molecular weight heparin
PE	pulmonary embolism
POC	Point of care
SAE	Serious adverse event
SEE	Systemic Embolic Events
SGOT	aspartate aminotransferase
SGPT	alanine aminotransferase
TIA	transient ischemic attack
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism

SYNOPSIS

Title of study	A Phase 3, Active (Warfarin) controlled, double-blind, double-dummy, randomized Study for assessing the efficacy and safety of rivaroxaban in patients with non-valvular Atrial Fibrillation.
Investigational Product	Rivaroxaban
Active Ingredient	5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
Study Phase	3
Research Hypothesis	Rivaroxaban is non-inferior to dose-adjusted warfarin for the prevention of the composite endpoint of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation
Primary Efficacy Objective	To determine if rivaroxaban is noninferior to warfarin (INR target range 2.0 - 3.0) in the combined endpoint of stroke (ischemic or hemorrhagic or unspecified type) and systemic embolism, in subjects with non-valvular AF who were at moderate-to-high risk for stroke
Primary Safety Objective	To demonstrate that rivaroxaban is superior to dose-adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

Secondary Objectives	• To compare rivaroxaban to warfarin with regard to the composite clinical outcome of stroke, non-CNS systemic embolism, and vascular death as well as each component separately. • To compare rivaroxaban to warfarin with regard to the composite of MI, non-fatal stroke, non-fatal SEE, and death due to cardiovascular cause or bleeding. • To compare the effects of rivaroxaban and warfarin with respect to disabling stroke (severity of strokes according to modified Rankin scale) and all-cause mortality • To evaluate the safety of rivaroxaban vs. warfarin with respect to: ✓ Individual bleeding event categories, ✓ All other clinical and laboratory safety assessments including liver enzyme and bilirubin abnormalities.
Study design	This is an event-driven, Phase 3, multi-center, randomized, double-blind, double-dummy, parallel-group study. The study will be divided into a screening period, a double-blind treatment period and a post-treatment observation period. To maintain the study blinding a double-dummy technique will be used. So with the use of an interactive voice response system, subjects will be randomly assigned in a 1:1 ratio to one of the following two groups: • subjects randomly assigned to rivaroxaban, will receive rivaroxaban 20 mg (or 15 mg for subjects with moderate renal impairment) plus warfarin placebo p.o. and • subjects randomly assigned to warfarin will receive warfarin titrated to a target INR of 2,5 plus rivaroxaban placebo p.o. Warfarin and its matching placebo will be dose-adjusted based on either real or sham INR results, respectively, which will be provided by a specially designed point-of-care INR device, so that the study blinding is

	protected.
Study Duration	This is an event-driven study. The study will continue until 445 primary endpoint events occur in the per protocol population.
Study Population	The study population consists of adults with documented non-valvular atrial fibrillation and a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus. Potential subjects who meet any of the following criteria will be excluded from participating in the study: hemodynamically significant mitral stenosis, prosthetic heart valve, planned cardioversion, increased bleeding risk (e.g. history of intracranial hemorrhage, known intracranial neoplasm or aneurysm or clinically significant gastrointestinal bleeding),planned major surgery, simultaneous treatment with both aspirin and a thienopyridine, severe renal insufficiency (calculated creatinine clearance < 30 mL/min), known significant liver disease, pregnancy or breast-feeding.
Statistical Methods	This is an event-driven trial that aims to establish that rivaroxaban is non-inferior to warfarin by a non-inferiority margin of 1.38 in terms of risk (hazard) ratio. This means that we need approximately 445 adjudicated primary efficacy events and about 14.834 patients (for a power of 90% and a confidence interval of 95%).An interim analysis will take place when either 50% of the primary efficacy events have occurred or at a maximum of 18 months after the first subject is randomized. The Cox proportional hazards Model with treatment as a covariate and a 2-sided 95% confidence interval for the hazard ratio rivaroxaban/warfarin will be used for the assessment of the primary efficacy endpoint in both the per protocol and in the intention-

	to-treat population, while on treatment. If non-inferiority for the primary efficacy endpoint is satisfied, then non-inferiority for the secondary efficacy endpoints on the per protocol population will be tested, using the same approach described above. If non-inferiority for each secondary efficacy endpoint on the per-protocol population is satisfied, then superiority for the respective secondary efficacy endpoint on the ITT population while on treatment will be tested. The principal safety endpoint is the composite of major and non-major clinically relevant bleeding events. Time from randomization to the first occurrence of a principal safety endpoint event will be analyzed based on the safety population while on treatment using the Cox Proportional Hazards model with treatment as a covariate.

1 INTRODUCTION

1.1 Backround

Atrial fibrillation is the most common cardiac arrhythmia of clinical significance and its prevalence increases with age, being less than 1% among people under 60 years of age with estimates of more than 6% among those over 80 years of age. It predisposes to the development of atrial thrombi, most commonly in the left atrial appendage, and for this reason atrial fibrillation is associated with an increase in the risk of ischemic stroke by a factor of four to five and it accounts for up to 15% of strokes in persons of all ages and 30% in persons over the age of 80 years. Vitamin K antagonists, such as warfarin, reduce the risks of stroke and death but increase the risk of hemorrhage as compared with control therapy. Therefore, warfarin is recommended for patients who have atrial fibrillation and are at risk for stroke.

Despite the established efficacy of vitamin K antagonists, they are cumbersome to use, because of their multiple interactions with food and drugs, and they require frequent laboratory monitoring. Therefore, they are often not used, and when they are, rates of discontinuation are high. Many patients receiving warfarin still have inadequate anticoagulation. Thus, there is a need for new anticoagulant agents that are effective, safe, and convenient to use.

Rivaroxaban is a highly selective oral direct factor Xa inhibitor that may provide more consistent and predictable anticoagulation than warfarin. It has been reported to prevent venous thromboembolism more effectively than enoxaparin in patients undergoing orthopedic surgery and was noninferior to enoxaparin followed by warfarin in a study involving patients with established venous thrombosis. This trial is designed to compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, who are at moderate-to-high risk for stroke.

1.2 Rivaroxaban

Activation of factor X plays a central role in the cascade of blood coagulation. Selective inhibition of FXa should inhibit thrombin generation and result in a potent antithrombotic effect. The inhibition of FXa for the treatment and prevention of thrombotic conditions is a well-validated approach. This mechanism has been successfully demonstrated by the low molecular weight heparins (LMWHs), enoxaparin in particular. Indeed, this therapy is currently indicated for the prevention of VTEs associated with orthopedic surgery and in high-risk patients during hospitalization , for the treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE) and for the prophylaxis of ischemic events in patients presenting with acute coronary syndromes.

1.2.1 Nonclinical Studies

In summary, preclinical pharmacology studies of rivaroxaban showed:

- Competitive, selective, direct inhibition of human FXa
- Inhibition of prothrombinase, with resultant anticoagulant activity, but no significant interaction with platelet function
- Species-dependent inhibition of FXa, with resultant antithrombotic activity in venous and arterial thrombosis models in rats and rabbits
- Excellent correlation between clotting times (e.g., PT) and plasma levels
- Antithrombotic activity without excessive prolongation of bleeding time in rats and rabbits
- Bleeding risk comparable with enoxaparin
- Co-administration of rivaroxaban with acetylsalicylic acid, naproxen, diclofenac, clopidogrel, or warfarin showed additive but not potentiating effects on bleeding time prolongation in the tail transection model in rats.

1.2.2 Clinical Studies

As of December 2005 a total of 33 Phase 1 studies involving 878 subjects have been conducted, with 735 subjects exposed to at least 1 dose of rivaroxaban and 143 to placebo. As of February 2006 a total of 2,232 subjects were exposed to rivaroxaban and 555 to the comparator enoxaparin in 4 completed Phase 2 studies for VTE prophylaxis after orthopedic surgery. In 1 completed Phase 2 study of DVT treatment, 883 subjects have been exposed to rivaroxaban and 263 to comparator drugs.

Phase 1 Studies

In the Phase 1 clinical pharmacology studies, rivaroxaban was well tolerated with no relevant safety parameters being affected in male volunteers, 18 to 45 years of age, at single doses up to 80 mg and multiple doses up to 30mg twice daily. In elderly subjects, no relevant safety parameters were affected after single dose administrations of 30 mg, 40 mg, and 50 mg rivaroxaban. Rivaroxaban does not influence bleeding time to a clinically relevant extent. Prolongation of PT is very closely correlated with plasma concentrations. Thrombin generation is inhibited dose dependently with all parameters being influenced (lag time, peak and total effect). Both pathways of coagulation (intrinsic and extrinsic) are affected.

Rivaroxaban pharmacokinetics are linear, with no relevant undue accumulation beyond steady state, which is achieved after 2 to 3 days.

Food increases the absorption of rivaroxaban by 30% for the area under the concentration versus time curve (AUC), independent of the food content, and decreases variability, whereas changes of gastric pH (ranitidine) or chelating drugs (Maalox) have no influence on pharmacokinetics and pharmacodynamics.

Inhibition of cytochrome 3A4 by ketoconazole results in an increase in plasma concentrations by about 2.6-fold for AUC.

Because approximately one-third of the administered rivaroxaban dose is excreted renally as unchanged drug, renal insufficiency is expected to affect drug elimination. Data from a phase I study showed an increase in rivaroxaban exposure correlated to decreased renal function, as assessed via creatinine clearance (CL_{CR}) measurements. In subjects with mild (CL_{CR} 50–80 mL/min), moderate (CL_{CR} 30–49 mL/min), and severe (CL_{CR} 15–29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4-, 1.5-, and 1.6-fold, respectively, compared with subjects with normal renal function. The increase in AUC was inversely correlated with the CL_{CR} rate, and there was a close correlation between the renal and total body clearance of rivaroxaban and the CL_{CR} rates of the subjects. Renal clearance decreased from 2.4 L/h in healthy subjects to 0.5 L/h in subjects with severe renal impairment. There are no data available for patients with CL_{CR} <15 mL/min.

Patients with mild hepatic impairment (classified as Child–Pugh A) exhibited only minor changes in the pharmacokinetics of rivaroxaban (i.e. an average of 1.2-fold increase in AUC), compared with the healthy control group. In patients with moderate hepatic impairment (classified as Child–Pugh B), there was an increase in rivaroxaban plasma concentrations and a prolonged elimination phase. In these patients, the AUC and C_{max} were increased by 2.3- and 1.3-fold, respectively, compared with healthy subjects. In addition, the elimination half-life was prolonged by approximately 2 h compared with healthy subjects.

Thus, in subjects with moderate to severe renal impairment and subjects with hepatic impairment (Child Pugh B), rivaroxaban plasma concentrations were significantly increased when compared with healthy subjects. In addition, FXa activity inhibition was significantly more pronounced and clotting tests showed prolongations compared with healthy subjects.

Therefore subjects with known significant liver disease and with severe renal impairment (calculated <30 ml/min) will be excluded from this study.

Phase 2 Studies

Currently, several Phase 2 studies have been completed evaluating the safety and efficacy of rivaroxaban compared with enoxaparin in the prophylaxis of VTE associated with total hip and total knee replacement surgery. In addition, one Phase 2 study has recently been completed comparing treatment with rivaroxaban to treatment with enoxaparin followed by 3 months of warfarin in subjects with symptomatic proximal venous thromboembolic disease.

Venous Thromboembolism Prevention Studies

In the Phase 2 dose-ranging studies ODIXa-HIP2 and ODIXa-Knee, 1,343 subjects were randomized to oral rivaroxaban at 2.5, 5, 10, 20, or 30 mg twice daily following hip or knee surgery, or subcutaneous enoxaparin (40 mg once daily starting 12 hours before hip surgery or 30 mg twice daily starting 12 hours after knee surgery), continuing until mandatory bilateral venography was performed 5 to 9 days after surgery. The primary efficacy endpoint was a composite of DVT, PE, and all-cause mortality. The primary safety endpoint was major postoperative bleeding. The combined analyses from these 2 studies showed that the primary efficacy endpoint occurred in 21.6%, 22.9%, 16.1%, 24.4%, and 19.3% of subjects receiving rivaroxaban 2.5, 5, 10, 20, and 30 mg twice daily, respectively, and 27.8% receiving enoxaparin (n=914). No significant dose-response relationship for efficacy was observed with rivaroxaban (P=0.39); this was potentially due to the efficacy achieved with the lower rivaroxaban doses. A significant dose response relationship was observed for major, postoperative bleeding with rivaroxaban (P<0.001), which occurred in 0.9%, 1.3%, 2.1%, 3.9%, and 7.0% of subjects receiving rivaroxaban 2.5-, 5-, 10-, 20-, and 30-mg twice daily, respectively, and 1.7% of subjects receiving enoxaparin (n=1,317). These studies demonstrated that rivaroxaban has a wide therapeutic window for the prevention of VTE following major orthopedic surgery, and, at doses of 2.5 to 10 mg twice daily, has similar efficacy and safety to the enoxaparin regimens.

Venous Thromboembolism Treatment Study

One Phase 2 study has been conducted in subjects with acute symptomatic DVT. This study (ODIXa-DVT) was a prospective, randomized, double-blind (for 4 different rivaroxaban doses), active-comparator controlled, multicenter, and multinational dose-finding study in 613 subjects with acute symptomatic DVT. The study assessed safety, tolerability, and efficacy of rivaroxaban at oral doses of 10, 20, and 30 mg twice daily and 40 mg once daily compared with enoxaparin/VKA in the treatment and secondary prevention of VTE. Study drugs were administered for 12 weeks. The primary efficacy endpoint was the response (improvement=thrombus regression) to treatment as determined by compression ultrasonography (CUS) after 3 weeks of treatment.

Thrombus regression as assessed by CUS (primary efficacy endpoint) was observed in 53%, 59%, 44%, and 57% of subjects receiving rivaroxaban 10 mg twice daily, 20 mg twice daily, 40 mg once daily, and 30 mg twice daily, respectively, compared with 46% for enoxaparin/VKA. There was no statistical evidence of a trend in the dose–response relationship between rivaroxaban and the primary efficacy endpoint.

The main safety endpoint in this study was the number of major bleeding events. The percentages of major bleeding events in the rivaroxaban dose groups ranged between 1.7 (10 and 20 mg twice daily and 40 mg once daily) and 3.3% (30 mg twice daily) compared with no events in the enoxaparin/VKA group; however, the differences between treatment groups were not statistically significant. It is important to note that there were no fatal bleedings or bleedings into critical organs in any of the treatment groups. This study supports evidence for the efficacy of rivaroxaban in the treatment of acute symptomatic DVT. The optimal net clinical benefit of rivaroxaban with regard to incidence rates of major VTE events and major bleeding events was obtained with rivaroxaban doses of 10 and 20 mg twice daily.

Comprehensive toxicological investigations of rivaroxaban have been performed. No clinicopathologic or histopathologic evidence of hepatotoxicity in any of the animal species tested (mice, rats, and dogs) has been observed.

In the Phase 1 program, a total of 735 subjects have been exposed to rivaroxaban. Eighteen subjects treated with rivaroxaban had elevated laboratory values (aspartate aminotransferase [AST]/alanine aminotransferase [ALT], gamma-glutamyl transferase, total bilirubin, amylase/lipase) postdose. None of these subjects presented a signal indicative of liver injury due to rivaroxaban. Often the peak elevation occurred several days to 1 week after a single dose of rivaroxaban. Values returned to normal or pretreatment levels, regardless of study drug discontinuation. No clinical concerns were raised based on these findings.

In the 4 completed Phase 2 VTE prophylaxis trials, a total of 2,232 patients had received rivaroxaban and 555 patients had received the comparator drug, enoxaparin. Three patients (0.2%) in the rivaroxaban group and 2 patients (0.5%) in the enoxaparin group had ALT levels 3 times greater than ULN plus total bilirubin levels 2 times greater than ULN during treatment. In these 5 cases the liver function test (LFT) abnormalities resolved spontaneously without discontinuing study drug.

In conclusion, although ALT values 8 times greater than ULN and ALT values 3 times greater than ULN in combination with bilirubin values 2 times greater than ULN have been observed in rivaroxaban-treated patients in the Phase 2 VTE prophylaxis program, such elevations have also been observed in the enoxaparin group. These elevations have not led to any clinically significant effects during the clinical development program.

Since currently approved anticoagulants (such as heparin and enoxaparin) and novel oral anticoagulants recently in development (e.g., ximelegatran) have been associated with LFT abnormalities, it would appear prudent to: continue to monitor LFTs closely in the ongoing rivaroxaban clinical programs including this one and to routinely collect samples for LFT testing during the treatment phase.

1.3 Warfarin

Warfarin is a synthetic derivative of dicoumarol, that acts by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K_1 to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Warfarin is indicated for the prophylaxis and/or treatment of VTE, PE, and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial infarction. The most serious risk associated with warfarin is hemorrhage in any tissue or organ. Treatment of each patient with warfarin is highly individualized and therefore, periodic determination of PT/INR is essential.

1.4 Rationale for the study

Patients with AF have a 5-fold increase in the risk of non-hemorrhagic stroke compared to patients in sinus rhythm. While oral VKAs can reduce the risk of stroke in such patients, the well known limitations (e.g., need for frequent monitoring of the level of anticoagulation), side-effects, and food/drug interactions of coumarin-derivatives provide a clinical opportunity for the development of safer, more effective, and simpler-to-use oral agents. Rivaroxaban has more predictable anticoagulant effect, does not require monitoring for blood tests, and has fewer drug/food interactions. If demonstrated to be as safe and effective as warfarin in this study, rivaroxaban would represent a potential alternative to VKAs in patients with AF.

This Phase 3 study is being conducted to demonstrate non-inferiority of rivaroxaban relative to warfarin (INR: 2.0 to 3.0, inclusive) in reducing the risk of stroke and/or SEE in subjects with documented non-valvular AF and in whom oral anticoagulation is indicated and planned for the duration of the study.

1.5 Rationale for Dose Selection

Rivaroxaban

Taking into consideration results of the dose-ranging Phase 2 VTE treatment studies that showed once and twice daily doses from 20 mg per day to 60 mg per day to be approximately comparable for efficacy and safety, the lowest tested dose of 20 mg once daily is selected for further evaluation.
Based on the expected differences in the pharmacokinetics between the populations of subjects with DVT and atrial fibrillation, it was decided to use a dose adaptation to 15 mg once daily for those subjects with moderate renal impairment at screening (defined as calculated CLCRbetween 30 and 49 mL/min, inclusive). Based on pharmacokinetic modeling this dose adaptation results in the same exposure (AUC), and hence can be analyzed as a single-dose-arm.

Warfarin

The warfarin dose will be selected by the treating physician to titrate the INR to a target of 2.5 (range 2.0 to 3.0, inclusive).

2 TRIAL OBJECTIVES AND HYPOTHESES

The primary objective is to compare rivaroxaban to warfarin and to demonstrate that its efficacy is non-inferior to that of dose adjusted warfarin in patients with non-valvular atrial fibrillation with regard to the composite primary endpoint of stroke and 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 end point is a composite of major and nonmajor clinically relevant bleeding events. Bleeding events involving the central nervous system that meet the definition of stroke will be adjudicated as hemorrhagic strokes and they will be included in both the primary efficacy and safety end points.

Secondary Objectives

1. To compare rivaroxaban to warfarin with regard to the composite clinical outcome of stroke, non-CNS systemic embolism, and vascular death as well as each component separately.
2. To compare rivaroxaban to warfarin with regard to the composite of MI, non-fatal stroke, non-fatal SEE, and death due to cardiovascular cause or bleeding.
3. To compare the effects of rivaroxaban and warfarin with respect to disabling stroke (severity of strokes according to modified Rankin scale) and all-cause mortality
4. To evaluate the safety of rivaroxaban vs. warfarin with respect to

- Individual bleeding event categories,

- All other clinical and laboratory safety assessments including liver enzyme and bilirubin abnormalities.

3 TRIAL DESIGN

This is a randomized, double-blind, double-dummy, parallel-arm study assessing rivaroxaban and warfarin with titration based on central monitoring of the international normalized ratio (INR). Subjects will receive active rivaroxaban tablets and placebo warfarin tablets or placebo rivaroxaban tablets and active warfarin tablets.

3.1 Details for the design of the trial

The study will be divided into a screening period, a double-blind treatment period closing with a study end visit, and a post-treatment observation period. At the study end 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 VKA or other appropriate therapy. Patients may discontinue study drug for any of the following reasons: safety concerns, pregnancy, stroke or systemic embolism, abnormal liver function, creatinine clearance <25 mL/min on 2 consecutive measurements, noncompliance, or the need for an excluded medication.

At the end of the post-treatment 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 445 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. Approximately 14.834 subjects are expected to enroll in this study.

Subjects will be qualified for the study within 15 days before randomization to allow adequate time for the site to review the inclusion and exclusion criteria for the prospective study participant. After meeting all study entry criteria, subjects will be randomized into treatment groups and begin study drug treatment. The randomization will take place with the use of an Interactive Voice Response System (IVRS) and subjects will be randomly assigned in a 1:1 ratio to 1 of the following 2 treatment groups:

- 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

OR

- 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 INR results will be generated by means of a validated algorithm reflecting the distribution of values in warfarin-treated patients with characteristics similar to those in the study population. The sham INRs will be based on real subject data that take previous treatment doses, age, and sex into account. A point-of-care coagulation testing device displays a code number that, when entered into the Interactive Voice Response System along with the subject's study identification number, is decoded and generates either the subject's real INR or a sham INR value, depending on the patient's blinded treatment.

During the study, INR monitoring occurs as often as clinically indicated but no less frequently than every 4 weeks. An unblinded physician, not affiliated with the conduct of the study, will monitor the warfarin management to ensure clinical sites respond to values out of range. Finally, the time in therapeutic range for the patients treated with warfarin will be reported at the conclusion of the study.

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.

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, unblinded INRs (i.e., not using the point-of-care device) should be performed every 1 to 2 days based on the initial INR.

Randomization of the subject should occur as soon as possible when the INR is ≤3.0.Randomization should occur within 36 hours of the last unblinded INR. Once the subject's eligibility for the study has been reconfirmed, the subject will be randomized (Day 1) and study drug will be dispensed.
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. A 12-lead electrocardiogram (ECG) and clinical laboratory tests will be performed annually.

All randomized subjects will be followed until the study ends (445 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 a study-end-visit. This visit should be completed as soon as possible, but within 30 days after site notification. At the study-end -visit, subjects will be transitioned from blinded study drug to an open-label VKA or other appropriate therapy and followed in the post-treatment observation period. The post-treatment observation period ends with a follow-up visit, which will be performed approximately 30 days after the study-end-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 the overall responsibility for the conduct and reporting of the study. An independent Data Monitoring Committee (DMC) will be commissioned for this study, in order to monitor the progress of the study and to ensure that the safety of the subjects is not compromised. 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.

The study design is presented below:

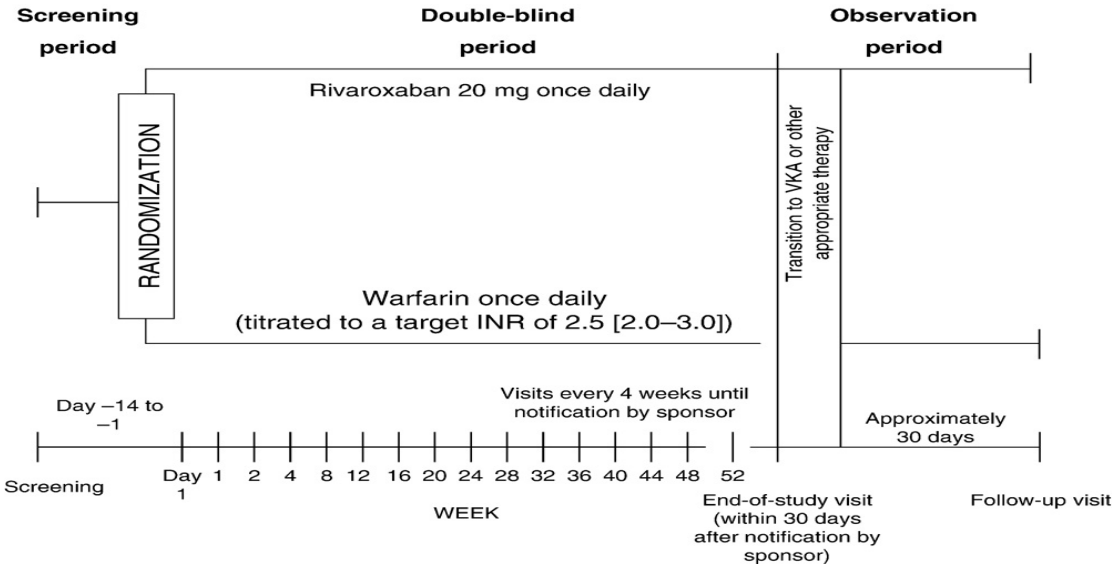

Figure 1 Plot summarizing the design of the study.

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3.2 Committees

3.2.1. Executive Committee

The EC consists of members of the academic leadership of the study and 1 member from the sponsoring company. The EC will ultimately be responsible for the conduct of the study including addressing any Data Monitoring Committee recommendations and overseeing publication of the results.

3.2.2. Steering Committee

A Steering Committee will be formed consisting of members who are lead investigators from each country/region. The Steering Committee will advise and assist the EC with regard to the scientific and operational aspects of the study.

3.2.3. Independent Data Monitoring Committee

This study will be conducted under the auspices of an independent Data Monitoring Committee (DMC), which will monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. The DMC will have a chairperson and include at least 2 cardiologists, a neurologist, as well as a statistician. This committee will review accumulating data on a regular basis, and may request to review partially unblinded or unblinded accumulating data. The DMC will make recommendations to the Executive Committee and Sponsor regarding the continuing safety of subjects currently enrolled and yet to be enrolled in the trial. At all times during the course of the study, the DMC may request access to unblinded data if needed.

3.2.4 Clinical Endpoint Committee

The Clinical Endpoint Committee (CEC), composed of experts in the relevant fields, will review, in a blinded manner, all reported study outcomes to provide consistency and validity in the assessment of outcomes. Their decisions will be based on blind clinical data. Their decisions will be used for the final statistical analyses.

4 ETHICAL CONSIDERATIONS

This study will be conducted in compliance with the protocol, the ethical principles set forth in the Declaration of Helsinki, the ICH Guideline E6 for GCP and applicable regulatory requirement(s). Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting research studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

4.1 Institutional Review Board/Independent Ethics Committee

The protocol and any amendments, the Investigator's Brochure, the subject informed consent and any information on compensation for study-related injuries or payment to subjects, will receive IRB/IEC approval prior to initiation of the study. During the study the investigator will send to the IRB any reports of adverse events that are serious, unlisted, and associated with the investigational drug and any new information that may adversely affect the safety of the subjects or the conduct of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task.

4.2 Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject or a legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered.

The written ICF should be prepared in the local language(s) of the potential subject population. The informed consent should be approved by the IRB prior to being provided to potential subjects.

The written informed consent form and any other written information to be provided to subjects should be revised whenever new information becomes available that may be relevant to the subject's consent. Any revisions to the written informed consent form and/or to other written information provided to the subject should be approved by the responsible IRB in advance of use.

Subjects unable to give their written consent (e.g., stroke subjects, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding.

If a subject or a subject's legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

Subjects may withdraw consent from participation in the study at any time. In the event a subject withdraws consent to receive study drug, the site may (with the subject's agreement) continue to contact the subject, general practitioner, and any other physician or medical care provider for the collection of outcome and survival follow-up data.

4.3 Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.
The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Sponsor personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

5 SELECTION OF SUBJECTS-STUDY POPULATION

The study population will consist of adult subjects with non-valvular atrial fibrillation who are at moderate to high risk for stroke and non-CNS systemic embolism.

5.1 Inclusion criteria

For entry into the study, the following criteria MUST be met.
1) Age ≥18 years

2) In atrial fibrillation or atrial flutter not due to a reversible cause and documented by ECG at the time of enrollment or within 30 days before randomization

3) Subjects with newly diagnosed atrial fibrillation are eligible provided that:

- there is ECG evidence on 2 occasions 24 hours apart demonstrating atrial fibrillation
- cardioversion is not planned

4) There must be evidence that the atrial fibrillation is NOT valvular

5) History of prior ischemic stroke, TIA or non-CNS systemic embolism believed to be cardioembolic in origin **OR** has 2 or more of the following risk factors:

- Age 75 years or older
- Diabetes mellitus
- Hypertension requiring pharmacological treatment
- Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with an LV ejection fraction (LVEF) ≤35 % by echocardiography, radionuclide study or contrast angiography

6) The number of subjects without a prior stroke, TIA or non-CNS systemic embolism and only 2 risk factors will be limited by the IVRS to approximately 10% by region of the total number of subjects enrolled.

7) Female subjects must be postmenopausal (for at least 2 years), surgically sterile, abstinent, or, if sexually active, they must be using an adequate method of contraception(e.g. oral contraceptives, intrauterine device, double-barrier method) to avoid pregnancy throughout the treatment period of the study or for 2 weeks after the last dose of study medication.

8) All subjects must provide **signed written informed consent**

5.2 Exclusion criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

1. hemodynamically significant mitral stenosis
2. prosthetic heart valve
3. Atrial fibrillation or flutter due to reversible causes (e.g. thyrotoxicosis, pericarditis)
4. Active infective endocarditis
5. Planned cardioversion

6. Increased bleeding risk that is believed to be a contraindication to oral anticoagulation, including but not limited to:
    - history of intracranial hemorrhage, known intracranial neoplasm or aneurysm
    - clinically significant gastrointestinal bleeding within 6 months before randomization
    - chronic hemorrhagic disorder
    - Platelet count ≤100,000/ mm^3
7. Planned major surgery
8. Required treatment with aspirin > 165 mg/day
9. Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel)
10. Severe renal insufficiency (calculated creatinine clearance < 30 mL/min)
11. Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3 x the ULN
12. Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, or diastolic BP > 100 mm Hg)
13. Active alcohol or drug abuse, or psychosocial reasons that make study participation impractical
14. Hemoglobin < 9 g/dL
15. Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole
16. Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin
17. Pregnancy or breast-feeding

5.3 Discontinuation of treatment-Withdrawal of Subjects

Individual subjects may prematurely discontinue study drug. Reasons for study drug discontinuation are:

- safety concerns (e.g adverse event, life threatening bleeding, abnormal liver function, creatinine clearance <25 mL/min on 2 consecutive measurements)
- pregnancy
- stroke or systemic embolism
- noncompliance with study drug
- the need for an excluded concomitant medication

A subject will be withdrawn from the study for any of the following reasons:

- withdrawal of informed consent form
- death
- lost to follow-up

In case a subject is lost-to-follow-up, every possible effort must be made by the study site personnel to contact the subject to obtain complete data and determine the reason for withdrawal. This reason should be documented on the CRF and in the source document.

Subjects, who discontinue treatment before the end of the study, and those who are withdrawn from the study, should have a follow-up visit approximately 30 days after the study drug discontinuation visit and they will be contacted every 3 months until the study ends to assess efficacy endpoint events.

6 RANDOMIZATION AND BLINDING

Central randomization will be implemented in conducting this study. At the time of enrollment, each subject will be assigned a unique sequential subject number by the IVRS (interactive voice response system) and a treatment code, which will dictate the treatment assignment for that subject. The IVRS will be available 24 hours per day, seven days a week. The subject number will consist of a unique 5 digit number which is assigned sequentially within the study (starting with 00001) by the IVRS. This number will be used for identification throughout the study and will not be used for any other subject. Subjects will be randomly assigned in a 1:1 ratio (rivaroxaban to warfarin) to 1 of 2 treatment groups and the randomization will be stratified by country, prior VKA use (defined as VKA use for 6 weeks or longer at the time of screening), and CHA_2DS_2-VASc risk score. So the IVRS will then also assign a medication kit (and subsequent medication kits) that matches the treatment code to which the subject has been randomized.

The investigator will not be provided with randomization codes. The codes will be maintained within the IVRS, which has the functionality to allow the investigator to break the blind for an individual subject.

This study has a double-blind and a double-dummy design. Neither the subjects nor any of the Investigators or Sponsor staff involved in the treatment or clinical evaluation of the subjects will be aware of the treatments received. There will be an independent DMC to monitor the data (bleeding AEs, liver enzymes and bilirubin abnormalities, SAEs, stroke, SEE) in an unblinded manner on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DMC.

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the subject. If for any reason, the Investigator needs to become unblinded to the treatment of a subject, he/she will make every attempt to first call the sponsor and discuss the need for unblinding and obtain agreement. If the investigator is unable to contact the sponsor, the investigator may in an emergency determine the identity of the treatment by telephoning IVRS. The sponsor must be informed as soon as possible by the investigator. Efforts should be made to limit access to knowledge of the treatment assignment to only those individuals who need to know the information and the subject should continue in the study.

Special blinding procedures

As it has already been stated, in order to ensure the study blinding, a double-dummy technique will be used so that similar dosing procedures can be followed in both treatment arms. This means that subjects randomly assigned to treatment *with rivaroxaban will also receive a placebo that is identical in appearance to warfarin, whereas subjects randomly assigned to treatment with warfarin will also receive a placebo that is identical in appearance to rivaroxaban.*

Rivaroxaban and its matching placebo will be taken once daily as a fixed dose. Warfarin and its matching placebo will be dose-adjusted based on either real or sham INR results, respectively. To accomplish this, all INR measurements will be performed using uniform POC (point of care) devices supplied to all study sites. The INR results generated by the POC device will be embedded in a “code number” and reported to a central IVRS along with the subject's study identification number. This code number is decoded by the Interactive Voice Response System, and either the subject's real INR or a sham INR value is generated, depending on the patient's blinded treatment.

In other words, for subjects randomized to warfarin, the true INR will be disclosed to allow the warfarin dose to be adjusted to maintain the INR between 2.0 and 3.0. Sham INR values will be given for subjects randomized to rivaroxaban to mimic variations expected for subjects on warfarin, so as to allow adjustments to the dose of placebo to match warfarin.

The measurement of the subject's INR and reporting in an unblinded fashion *will NOT be permitted* during the treatment period. The study site personnel should use ONLY the study-provided POC device for INR assessments at all times after a subject begins study drug treatment.

7 STUDY PROCEDURES

The study is divided into 3 periods: a screening period, a double blind treatment period and a post-treatment observation period. All randomized subjects will be followed until the study ends, even if they did not take study drug or prematurely discontinued study drug.

7.1 Screening period

As part of study qualification which takes place before randomization, potential subjects will have the study risks and benefits explained to them, the associated ICF reviewed with them, and all questions answered for them. Before the performance of any protocol-specific procedure, written informed consent should have been obtained by the investigator.
Screening procedures will be performed within 15 days before randomization. The investigator should obtain relevant medical history and vital signs and perform physical examination. A 12 lead ECG and clinical laboratory tests (including urine pregnancy test) should also be performed.
The results of all screening procedures must be reviewed before randomization to ensure that all inclusion criteria and none of the exclusion criteria are met.
Eligible subjects will be instructed to return for a baseline visit (Day 1) on the day of planned randomization. Subjects who are on chronic therapy with a VKA must discontinue it once eligibility is confirmed; these subjects must have their randomization (Day 1) visit performed as soon as possible when the INR is ≤3.0

7.2 Treatment period

7.2.1. Day 1 –randomization

Eligible subjects will be randomized to study medication using an IVRS as described in section 6(Randomization and blinding) and study drug will be administered. The subjects should start taking study drug with food in the evening of the same day.

7.2.2. Monthly visits

Subjects will return for visits at week 1, 2, 4 and then every 4 weeks during the double-blind treatment period. (Additional interim visits may be scheduled, at the Investigators discretion, if necessary for INR monitoring)

During these visits:

- the INR should be assessed using the point of care device provided by the Sponsor for adjustment of warfarin (or placebo-to-match warfarin) doses(instructions for INR monitoring are provided in sections 3, 6 and 8)
- adverse events should be recorded
- efficacy endpoint events should be assessed
- study drug should be dispensed, as needed
- unused study drug tablets should be counted
- targeted concomitant medications should be recorded
- vital signs should be recorded
- Liver function tests-SGOT, SGPT, γgt, ALP, Total bilirubin- should be performed on week 4 and every 4 weeks thereafter
- A 12 lead ECG will be performed annually

7.2.3. Study drug discontinuation visit

Individual subjects may prematurely discontinue study drug. Reasons for study drug discontinuation are: safety concerns, life threatening bleeding, pregnancy, stroke or systemic embolism, abnormal liver function, creatinine clearance <25 mL/min on 2 consecutive measurements, noncompliance, the need for an excluded medication or withdrawal of informed consent.

They should have a follow-up visit approximately 30 days after the study drug discontinuation visit and they will be contacted every 3 months until the study ends to assess efficacy endpoint events.

In case a subject is lost-to-follow-up, every possible effort must be made by the study site personnel to contact the subject to obtain complete data and determine the reason for withdrawal. This reason should be documented on the CRF and in the source document.

7.2.4. Study end visit

The study end visit will occur within 30 days after the prespecified number of adjudicated primary endpoint events has occurred, and is defined as the last visit in the double-blind treatment period for subjects on study drug at that time. All randomized subjects, including those who temporarily interrupted or discontinued study drug, will have a study end Visit. The study end visit activities include:

- physical examination, vital signs, 12-lead ECG
- Record AEs and endpoint events
- Record date/time of final dose of study drug
- Contact IVRS to record subject as having completed study end Visit

After the final dose of study drug, the Investigator at his/her discretion will prescribe open-label antithrombotic therapy as per local guidelines. When subjects transition from blinded study drug to open-label warfarin (or other VKA) at the final visit, it is important to maintain the study blind to avoid the introduction of bias in the ascertainment of study endpoints. For this reason no INR measurements should be performed in the first three days after the final dose of blinded study drug.

7.3 Post-treatment observation period- follow-up visit

After the study end visit or Study drug discontinuation visit, there will be an observation period to follow subjects after transition from study drug to open-label VKA or other appropriate therapy. Subjects will return to the clinic for a follow-up visit approximately 30 days after the permanent discontinuation of study drug.
At the follow-up visit the Investigator will:

•Assess for SAEs (until 30 days after the last dose of double-blind study drug)

•Assess for outcomes (death, stroke, systemic embolism, myocardial infarction)

7.4 Efficacy Assessments

7.4.1 Primary Efficacy Assessments

The primary efficacy endpoint of the study will be the time to the first occurrence of confirmed stroke (hemorrhagic, ischemic or of unspecified type) or systemic embolism. An independent blinded Clinical Endpoint Committee will apply the protocol definitions and adjudicate and classify the following endpoints:

Stroke: Stroke is defined as an abrupt onset of focal neurological symptoms resulting from a presumed cerebrovascular cause and lasting at least 24 hours, which are not due to a readily identifiable cause such as a tumor or seizure.

If an event matching this definition lasts less than 24 hours it will be considered a TIA.

It is strongly recommended that an imaging procedure such as a CT scan or MRI be performed. All strokes will be classified by the CEC as ischemic, hemorrhagic or type uncertain.

Subjects who die within 30 days of the onset of the stroke will be regarded as having had a fatal stroke.

Non-CNS systemic embolism: is defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy.

7.4.2 Secondary Efficacy Assessments

Myocardial infarction: The following criteria satisfy the diagnosis for an acute or evolving MI in an appropriate clinical context:

- elevation of CK-MB or Troponin T or I ≥2 ×the ULN, or
- if no CK-MB or troponin values are available, a total CK ≥2×ULN, or
- new, significant (≥0.04 s) Q waves in ≥2 contiguous leads

Vascular Death: This category includes cardiac deaths (e.g., cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other cardiovascular deaths (stroke, pulmonary embolism, ruptured aortic aneurysm or dissection)

7.5 Safety Assessments

The principal safety end point is a composite of major and non-major clinically relevant bleeding events

Major Bleeding: clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death

Non-major clinically relevant bleeding: clinically overt bleeding that does not satisfy the criteria for major bleeding and that leads to hospital admission, physician-guided medical or surgical treatment, cessation of study treatment or any other change in antithrombotic therapy.

8 GUIDELINES FOR SUBJECT MANAGEMENT

8.1 Invasive Procedures and Surgery

It is anticipated that subjects enrolled in this clinical study may require invasive procedures. Study drug may be interrupted as necessary for these invasive procedures or as medically needed, taking into account the risk to the subject. For subjects with an intermediate or high risk of thromboembolism, warfarin/warfarin placebo should be discontinued approximately 4 days in advance of the procedure and rivaroxaban/rivaroxaban placebo approximately 2 days before. INRs using the point-of-care device should be performed daily or at the discretion of the investigator. When the INR is ≤1.5, the elective procedure may be performed. The physician may consider administration of low dose unfractionated heparin or prophylactic dose LMWH (e.g., enoxaparin 40 mg subcutaneous injection daily) beginning 2 days preoperatively. When hemostasis is secure and the subject is able to safely ingest oral medication, study drug should be resumed and daily INRs using the point-of-care device should be performed.

For urgent or emergent invasive procedures, when waiting 4 - 5 days is not an option, management will in part depend on the randomized treatment assignment (warfarin or rivaroxaban) and unblinding may be necessary.

8.2 Bleeding events

Bleeding is of special interest because such events are a known concern associated with anticoagulant therapy including rivaroxaban and warfarin. All bleeding events either reported by the subject or observed by the Investigator should be recorded on the CRF, along with the date and time of onset. Clinically overt bleeding events requiring medical attention will be adjudicated by an independent and blinded Clinical Endpoint Committee.

For subjects with minor bleeding, study drug may or may not be held at the discretion of the local physician and investigator, after a risk/benefit determination has been made.

However, if a subject has a clinically significant bleeding event during study treatment, the study *drugs should generally be held* (rivaroxaban has a half time of 5 to 13 hours) and the following routine measures could be considered:

- Volume resuscitation, and transfusion of blood products as appropriate
- Warfarin can be reversed more quickly by giving oral or intravenous vitamin K, and/or with fresh frozen plasma

There is no reversal agent for rivaroxaban. Given its half-life (5 - 13 hours), however, the anticoagulant effect of rivaroxaban abates in 24 - 48 hours.

8.3 Treatment Guidelines for Jaundice, Elevated LFTs

Liver function is another area of special interest. If at any time during the treatment period a subject's liver function test (LFT) results show elevated ALT> 3 ULN and/or total bilirubin > 2 ULN, the following laboratories should have been obtained/retested within the subsequent 5 days: : ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, CPK . The treating physician may continue the study drug during this time. If the repeat value is lower, weekly ascertainment of ALT, AST, total and direct bilirubin, and alkaline phosphatase will be performed until the ALT is <3 x ULN. If the repeat

ALT ≥3x ULN AND the total bilirubin is ≥2 x ULN and this persists for more than one month, then study medication must be ***discontinued*** and hepatitis screen (anti-HAV, HbsAg, anti-HBc, anti-HBs and anti-HCV) and abdominal ultrasound have to be performed.

8.4 Treatment Guidelines for patients with renal impairment

As it has already been mentioned, subjects with severe renal insufficiency (calculated creatinine clearance < 30 mL/min) will be excluded from the study.

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.

If the calculated CLCR becomes <25 mL/min (confirmed by repeat assessment) during the study, then study medication should be discontinued.

For subjects who start with a calculated CLCR of ≥50 mL/min and the CLCR decreases to below 50 mL/min during the study, no dose adjustment will be performed.

9 INFORMATION ABOUT TREATMENTS ADMINISTERED

9.1 Study drugs description-drug accountability

The Investigator must ensure that the Investigational Product will be used only in accordance with the protocol. Subjects will be randomly assigned to 1 of 2 treatment groups:

• 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
OR
• 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

Subjects should be instructed to take the study drug in the evening with food.

The study drugs will be supplied by the Sponsor and they should be stored at room temperature (22-25 ºC) in a secure, limited-access storage area, protected from light .They will be sent to the investigational sites, and the Investigator will be responsible for dispensing them, providing the subjects with sufficient study drug until the next scheduled study drug dispensing visit. Subjects must be instructed to return all original containers, whether empty or containing study drug. Returned study drug must not be dispensed again, and should be disposed of according to the sponsor's instructions.

9.2 Concomitant Therapy

All medications taken by each subject will be recorded on the CRF.

9.2.1 Restricted agents:

- It is strongly encouraged to restrict the dose of aspirin (if indicated) to ≤100 mg daily, although higher doses are permitted for a strong clinical indication (e.g., development of an acute MI).
- Chronic use of non-steroidal anti-inflammatory drugs (more than 10 consecutive days) should be avoided
- Concomitant use of both aspirin (≤165 mg/day) and a thienopyridine (e.g. clopidogrel) together with study drug should be avoided .At the time of acute coronary syndrome the decision to employ dual antiplatelet therapy in subjects on study drug may arise. Because there are only few data from randomized clinical trials of dual anti-platelet therapy in the setting of oral anticoagulation, and there is a heightened concern regarding bleeding, this decision should be made carefully by the investigator, after having weighted the risks and the potential benefits.

9.2.2 Prohibited Therapy

The following drugs CANNOT be used during the treatment period, unless no alternative therapy is clinically suitable. In case any of the following medications is clinically necessary, the study drug should be temporarily interrupted:

- Fibrinolytic agents, if required to treat acute MI or PE, require study drug interruption
- Systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as atazanavir, clarithromycin or ketokonazole
- Treatment with a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin, phenytoin or phenobarbital

10 STATISTICAL CONSIDERATIONS

The primary efficacy endpoint will be the time to first occurrence of confirmed ischemic stroke, hemorrhagic stroke, stroke of unspecified type or systemic embolism.

H0: RR $\geq \Delta$

Versus

H1: RR $< \Delta$,

Where:

- RR represents the risk of rivaroxaban relative to warfarin
- H_0 (the null hypothesis): rivaroxaban is *less* effective than vitamin K antagonists in reducing thromboembolic events (*it is inferior*).
- H_1 (the alternative hypothesis): rivaroxaban is *at least* as effective as vitamin K antagonists in reducing thromboembolic events (*it is not inferior*).

10.1 Sample size determination

10.1.1 Noninferiority margin

A key aspect of developing the adequate sample size for this trial is arriving at the appropriate non-inferiority margin

Noninferiority trials without a placebo arm often require an indirect statistical inference for assessing the effect of a test treatment relative to the placebo effect or relative to the effect of the selected active control treatment. The indirect inference involves the direct comparison of the test treatment with the active control from the noninferiority trial and the assessment, via some type of meta-analyses, of the effect of the active control relative to a placebo from historical studies.

Warfarin has been studied in 6 different placebo controlled randomized trials in subjects with AF. These studies are described by J. Lawrence along with the details of a meta-analysis for the studies. In the 6 trials, the overall Relative Risk (RR) for warfarin vs placebo was 64% (95% CI 47%-76%). Each of the trials was terminated early owing to efficacy or results of publications demonstrating the superiority of warfarin to placebo. These early terminations may have led to some degree of overestimation of the magnitude of treatment effect and resulted in wide CIs for the estimates in each study.

Although the efficacy and safety of warfarin treatment in AF are consistent across the historical placebo-controlled trials, an equally important question is how relevant these trials are to contemporary clinical practice. Older trials were conducted in the context of very different care (such as less emphasis on blood pressure control), with different standards for warfarin use (such as lack of standard target INR across trials), with combination of open-label and blinded designs, and with differing primary outcomes, durations of treatment, and quality of follow-up. Thus, although the overall data show a clearly substantial benefit to VKA versus placebo in preventing stroke, the exact degree of benefit and confidence thereof are uncertain, which provides an unstable foundation for establishing the degree of benefit one needs to preserve with an alternative antithrombotic.

All of these factors argue that standards should be high in noninferiority trials, which necessarily use historical controls to establish the treatment effect to be shown to be preserved.

In the case of warfarin for AF, the treatment effect from prior trials is robust and consistent even given their limitations, thus providing high confidence in the benefits of warfarin. The Relative Risk Reduction (RRR) of warfarin compared with placebo in these trials using a random effects model was 0.36 (95% CI 0.24-0.53), such that the inverse of the upper boundary (i.e., control compared with warfarin) is 1.88 (1/0.53).

The noninferiority margin is determined by halving the control effect, based on a historical placebo-controlled trial. This type of "discounting" is applied to protect against lack of "constancy", that is, conditions in the planned non-inferiority study have changed from the historical meta-analysis data. To establish that at least half of the warfarin effect is preserved, the noninferiority margin is 1.38 (i.e., the margin is the midpoint between 1.0 and 1.88 on a log scale rather than linear scale because the primary parameter estimated is the logarithm of the relative risk)
In other words **if we want to show that rivaroxaban maintains at least half of a conservative estimate of the historical benefit of warfarin relative to placebo, then the upper limit of a two-sided CI for the relative risk of rivaroxaban versus warfarin must be less than 1.38.**

10.1.2 Determination of sample size-number of events

When the end point is measured as the time to the event rather than the event rate, the number of events needed for a 1-side level-α test to detect a hazard ratio ρ with 1−β power is then given by:

$$D = 4\left[\frac{z_\alpha + z_\beta}{\ln(\rho)}\right]^2$$

So in this case if we want a 95% confidence interval and the power is 90%, we have:

$D=4\ (1{,}96+1{,}28/\ln\ (1{,}38))^2=404{,}81$

So based on the above assumptions, we need at least 404,81 primary efficacy endpoints. Increasing this number by approximately 10% to 445 will provide a more robust number of events to assess consistency across important subgroups.

The total number of randomized subjects for obtaining 445 adjudicated events from the per protocol population is calculated based on the following assumptions:

- Warfarin treatment group event rate of 2.3% per patient-year (This event rate was adjusted for patients with high risk that are likely to present according to the inclusion criteria)
- The mean time on treatment(either warfarin or study drug) and follow up will be 18 months(1,5 years)
- Expected dropout (withdrawal of consent, lost to follow-up, premature discontinuation of study drug) rate of 15%.

This means we need 445/0,023 =19.348 patient-years or (due to the fact that the mean time on treatment (either warfarin or study drug) and follow up is expected to be 18 months (1,5 years)), we need 19348/1.5=12899 patients.
Moreover, if we want to compensate for the expected dropout as mentioned above, we have to increase this number by 15%.So finally we need ***at least 14.834 patients for an expected number of 445 primary endpoints***.

10.2 Analysis Populations

The per protocol population includes all randomized patients excluding those who have specific pre-defined major protocol deviations that occur by the time of enrollment into the study or while they are on treatment and before they experience a primary efficacy endpoint event. The protocol deviations mentioned above include:

- No proper informed consent
- Inadequate documentation of atrial fibrillation at the time of enrollment into the study
- Prosthetic heart valve
- Receiving study medication different from that assigned by the IVRS
- Not receiving any study medication during the double-blind treatment period

On treatment: A study subject is considered to be on treatment during the period from the first double-blind study medication administration until the final dose of study drug, the study-end-visit or death, whichever comes first. During a study drug interruption or discontinuation, the subject is considered at risk during the first two days, even though the subject is not on study drug, to allow consideration for any carryover effects.

Intention-to-treat population includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence to the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. So everyone who will be randomized in the trial will be considered to be part of the trial regardless if he or she has completed the trial.

All ITT analyses will be performed based on the on-treatment ITT population and will evaluate time while on study drug till 2 days after permanent discontinuation.

Safety Analysis population: All randomized subjects who receive at least one dose of randomized study drug. Analyses will be based on the randomized treatment unless a subject inadvertently receives the incorrect drug during the entire study, in which case, the subject will be grouped according to the treatment actually received.

All safety analyses will be performed based on the safety population while on treatment.

The ITT population, while on treatment and the Per Protocol population will be included in the primary efficacy analysis for non-inferiority. The Per Protocol population will be included in the secondary efficacy analyses for non-inferiority. The ITT population, while on treatment will be included in the secondary efficacy analyses for superiority.

The safety analysis population will be included in the safety analyses.

All analyses will be performed on observed data only. No missing data will be imputed. Only events confirmed by the Clinical Endpoint Committee will be included in the analyses. Data on subjects who do not reach the primary endpoint will be censored at the earlier of their death date (when death is not part of the endpoint) or last contact date (for subjects who withdraw consent to be followed up or are lost to follow-up).

10.3 Primary Efficacy Analysis

The primary hypothesis is that rivaroxaban will be noninferior to warfarin for the prevention of stroke or systemic embolism. The ITT population, while on treatment, and the Per Protocol population will be included in the efficacy analyses for non-inferiority.

The time to first event is defined as the time (years) at risk from the initial dose of study drug to the first event experienced by a subject while at risk. The subject is at risk while taking study drug. During a study drug interruption or discontinuation, the subject is considered at risk during the first two days even though the subject is not on study drug to allow consideration for any carryover effects. The events occurring during such study drug interruptions/discontinuations (except for events occurring during the first two days) will not be included in the primary analysis.

For subjects who do not experience an event while at risk, the time to first event will be censored at 2 days after the final dose, the study-end-Visit or the subject's last assessment while at risk.

To ascertain non-inferiority, it will be necessary to demonstrate that the rivaroxaban event rate for the primary endpoint is not substantially higher than the warfarin event rate as measured by the hazard ratio (or relative risk) of rivaroxaban relative to warfarin. So based on time from randomization to the first occurrence of a primary efficacy endpoint event, the objective of the primary efficacy analysis is to establish that rivaroxaban is noninferior to warfarin by a non-inferiority margin of 1.38 in terms of risk ratio.

The time to first event will be analyzed using the **Cox Proportional Hazards Model** with treatment as a covariate and a 2-sided 95% confidence interval for the hazard ratio rivaroxaban/warfarin. If the upper limit of this 2-sided confidence interval is below the non-inferiority margin of 1.38, then non-inferiority of the study drug can be declared.

Additional analyses will be made using 3 stratification factors, one at a time: region-country, prior VKA status (experienced or naïve) and history of prior stroke.

If non-inferiority for the primary efficacy endpoint on the per-protocol population is satisfied, then non-inferiority for the primary efficacy endpoint on the ITT population while on treatment will be tested, using the same approach described above.

Furthermore, cumulative event rates of the primary efficacy endpoint over time will be estimated using the **Kaplan-Meier method.**

10.4 Subgroup Analyses

In order to test for homogeneity of treatment effect across subgroups as far as the primary efficacy endpoint is concerned, the following subgroups will be examined using the Cox proportional Hazards Model:

- Geographic Region
- CHA2DS2-VASc Score
- History of prior stroke or TIA
- Sex
- Race (Caucasian, Asian, Black)
- Renal function (CLCR<50 or ≥50)
- Prior VKA use (defined as VKA use for 6 weeks or longer at the time of screening)
- Age (≤64, 65-75, >75)

10.5 Secondary Efficacy Analysis

Secondary efficacy endpoints will be analyzed based on the Intention-to-treat population, while on treatment. If non-inferiority for the primary efficacy endpoint is satisfied, then non-inferiority for the secondary efficacy endpoints on the per protocol population will be tested. The non-inferiority margin will be the same (1,38) as that for the primary efficacy non-inferiority analysis.

The first secondary endpoint is the composite of stroke, non-CNS systemic embolism, and vascular death. The time to first event is defined as the time (years) from the day of randomization to the first event experienced by a subject. The time to first event (an event of stroke, SEE, or death) will be estimated by a Kaplan-Meier estimate and will be compared between rivaroxaban and warfarin using Cox Proportional Hazards Model at a significance level of 95%.

The other secondary endpoint is the composite of MI, non-fatal stroke, non-fatal SEE, and death due to cardiovascular cause or bleeding. The time to first event will be estimated by a Kaplan-Meier estimate and will be compared between rivaroxaban and warfarin using Cox Proportional Hazards Model at a significance level of 95%.

Similarly, the other secondary efficacy endpoints (mentioned on Section 2) will be assessed.

If non-inferiority for each secondary efficacy endpoint on the per-protocol population is satisfied, then superiority for the respective secondary efficacy endpoint on the ITT population while on treatment will be tested.

10.6 Safety Analysis

The Safety Analysis population consists of all randomized subjects who receive at least one dose of randomized study drug. The term "on treatment" refers to the period between the first administration of study drug and two days after the last administration of study drug. (See section 10.2). This period will be the basis for the safety analysis.

10.6.1 Primary Safety Analysis

The principal safety end point is a composite of major and nonmajor clinically relevant bleeding events. Bleeding endpoints will be presented as rates/100 patient-years of follow-up. 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. All analyses of rates of bleeding will be based on the first event in the safety population during treatment. The Cox Proportional Hazards Model with treatment as a covariate will be used and the estimate together with the 95% confidence interval will be provided. Kaplan-Meier methodology will be used to estimate cumulative event rates over time. Subjects without events during the treatment period will be censored.

10.6.2 Subgroup Safety Analysis

In order to test for homogeneity across subgroups as far as the primary safety endpoint is concerned, the Cox model will also be used to compare patients with major and nonmajor clinically relevant bleeding events in terms of demographic and clinical characteristics; for each characteristic, a univariate Cox model for the risk of major bleeding will be derived. The following candidate variables will be included: Hypertension, Abnormal renal/liver function, history of Stroke, Bleeding history, Drugs/alcohol abuse, age ,sex, use of aspirin and prior peptic ulcer disease.

10.6.3 Secondary Safety Analysis

The incidence of confirmed major bleeding events, confirmed clinically relevant non-major bleeding events, minor bleeding events and all bleeding AEs occurring throughout the treatment period will be summarized by treatment group and analyzed separately using the methodology described above.

Furthermore, the number and percentage of subjects with persistent elevation of liver enzymes (ALT, AST) and TBL will be summarized by treatment regimen.

Moreover, incidences of treatment-emergent adverse events and serious adverse events will be compared between the treatment groups based on non-stratified analysis. Logistic regression models will be used, if required, to adjust for confounding factors.

10.7 Interim Analysis

An interim analysis will be performed, when either 50% of the primary efficacy endpoint events, as reported by the Clinical Endpoint Committee (CEC), have occurred, or at a maximum of 18 months after the first subject is randomized. The purpose of this interim analysis is to stop the study early if it is unlikely to establish non-inferiority for the primary efficacy endpoint, if the study were to run to completion. In other words the objective of the interim analysis is to stop the study early due to lack of efficacy. The study will NOT be terminated early to declare non-inferiority.

11 ADVESE EVENTS

11.1 Definitions

An Adverse Event (AE): is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment

Serious Adverse Event: A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

11.2 Severity of Adverse Event

- Mild (Grade 1) - Awareness of event but easily tolerated
- Moderate (Grade 2) - Discomfort enough to cause some interference with usual activity
- Severe (Grade 3) - Inability to carry out usual activity
- Very Severe (Grade 4) - Life-threatening or disabling AE

11.3 Adverse Event Documentation-Reporting

Subjects must be carefully monitored for adverse events. All adverse events occurring after the subject has signed the informed consent form must be fully recorded in the subject's CRF. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.
Serious adverse events must immediately (within 24 hours of the investigator's awareness) be reported and must be followed up until resolution or stabilization. If required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

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