UNIVERSITY OF THESSALY

SCHOOL OF MEDICINE

MASTER PROGRAM IN
Methodology of Biomedical research, Biostatistics and clinical Bioinformatics

Master Course Thesis

<< Protocol for a Phase 3, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of Apixaban In Preventing Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation >>

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Larissa, Greece, August 2015

SYNOPSIS

Clinical Protocol

Title of Study: A Phase 3, Active (Warfarin) Controlled, Randomized, Double- Blind, Parallel-Arm Study to Evaluate Efficacy and Safety of Apixaban In Preventing Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

Study Phase: 3

Research Hypothesis: Apixaban is noninferior to warfarin for prevention of stroke (ischemic or hemorrhagic or of unspecified type) or systemic embolism in subjects with atrial fibrillation (AF) and additional risk factor(s) for stroke.

Primary Objective: To determine if apixaban is noninferior to warfarin (INR target range 2.0 - 3.0) in the combined endpoint of stroke (ischemic or hemorrhagic or of unspecified type) and systemic embolism, in subjects with AF and at least one additional risk factor for stroke.

Key Secondary Objectives: To determine, in subjects with AF and at least one additional risk factor for stroke, if apixaban is superior to warfarin (INR target range 2.0-3.0) for

- The combined endpoint of stroke (hemorrhagic, ischemic, or of unspecified type) and systemic embolism,
- Major bleeding (ISTH)
- All-cause death.

Study Design: Randomized, double-blind, double-dummy, parallel-arm study assessing apixaban and warfarin with titration based on central monitoring of the international normalized ratio (INR). Subjects will receive active apixaban tablets and placebo warfarin tablets or placebo apixaban tablets and active warfarin tablets.

Screening Period: The protocol includes a screening period of up to 14 days; subjects who meet the inclusion / exclusion criteria are eligible. Subjects with AF and at least one additional risk factors for stroke will be evaluated for study eligibility. Emphasis will be placed on recruiting both warfarin-naïve and warfarin-experienced subjects. Vital signs, a 12 lead electrocardiogram (ECG), and clinical laboratory samples will be obtained during this period.

Treatment Period

Treatment Visits: Study visits will occur monthly for INR monitoring. At the INR visits, only INR monitoring, assessment of outcomes, assessment of AEs, and assessment of study medication compliance will be performed. In addition, at the quarterly visits during the treatment period (Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54 and 57) assessment of changes in concomitant medications, vital signs and laboratory assessments will be performed and at the yearly visits during the treatment period (Months 12, 24, 36 and 48) physical measurements, and 12 lead ECGs will be obtained. All subjects will be followed for the development of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, myocardial infarction, death, bleeding, hospitalization or treatment discontinuation until the end of the study.
Subjects will receive either apixaban and warfarin-placebo or apixaban-placebo and warfarin following randomization during a titration phase using a dosing algorithm consisting of two initial daily doses warfarin (or warfarin-placebo) with a target INR range 2.0 to 3.0. and doses of apixaban (or apixaban-placebo) of either 5 mg BID or 2.5 mg BID.
Subsequent warfarin doses will be recommended based upon an algorithm, however, the final decision as to dose will rest with the investigator. INR monitoring will begin by the fourth day following initiation of drug administration and will be performed twice a week for two weeks, once a week for two weeks, and monthly thereafter once a stable INR is attained. An investigator may increase the frequency of INR monitoring if it is considered clinically indicated, with titration of warfarin or warfarin-placebo based on central monitoring of INR measurements utilizing encrypted point of care (POC) devices and centralized dosing recommendations.
For certain subjects who may be deemed to be at higher risk of bleeding with study drug (e.g., the elderly, small stature, renal impairment), a lower dose of apixaban (2.5 mg BID) will be used. Subjects who fulfill any two of the following criteria will have their apixaban dose reduced to 2.5 mg BID at the time of randomization only:
• Age $\geq$ 80 years
• Body weight $\leq$ 60 kg
• Serum creatinine $\geq$ 1.5 mg/dL

Follow-Up Period

Follow-up Visits: Follow-up of subjects who discontinued study drug prior to the attainment of 433 primary efficacy events in the study should occur quarterly by a telephone call; the final follow-up visit should be in person, if at all possible, and should be performed within approximately 30 days after the attainment of 433 primary efficacy events in the study. Subjects who completed double-blind treatment with study drug should have a telephone contact approximately 30 days after the last dose of double-blind study drug. SAEs (that occurred within 30 days after the last dose of double-blind study drug) and study outcomes will be documented at all follow-up contacts.

Randomization: Eligible subjects will be randomized in a 1:1 ratio to either apixaban or warfarin titrated to a target INR range 2.0 to 3.0. Subjects who are on warfarin or another Vitamin K antagonist (VKA) prior to randomization will have their VKA discontinued prior to randomization. Each arm will contain 7,843 subjects. The randomization will be stratified by investigative site and prior warfarin/VKA status (experienced, naïve). A subject will be classified as warfarin naïve if they have not previously received warfarin or another VKA or have received $\leq$ 30 consecutive days of treatment with warfarin or another VKA in the past. Otherwise the subject will be classified as warfarin experienced.

Duration of Study: The expected duration of the study, from first subject, first visit through the last follow-up phone contact for the last subject, is approximately 60 months.

Number of Subjects per Group: 15.68**6** subjects (7.843 subjects for each treatment group).

Study Population: Males and females ≥ 18 years of age with AF and one or more of the following additional risk factors for stroke: (1) age ≥ 75 years, (2) previous stroke, transient ischemic attack (TIA) or systemic embolism (SE), (3) symptomatic congestive heart failure or left ventricular dysfunction with an LVEF ≤ 40%, (4) diabetes mellitus, or (5) hypertension requiring pharmacological treatment.

Test Product, Dose and Mode of Administration, Duration of Treatment: Oral apixaban 5 mg or 2.5 mg tablets given BID or matching placebo for the treatment period (average of 2.3 yrs of follow-up from randomization).

Reference Therapy, Dose and Mode of Administration, Duration of Treatment: Oral warfarin dose titrated to a target INR range of 2.0 - 3.0 or matching placebo for the treatment period (average of 2.3 yrs of follow-up from randomization)

Criteria for Evaluation

Primary efficacy endpoint

The primary efficacy endpoint is the time to first occurrence of confirmed stroke (ischemic, hemorrhagic, or of unspecified type) or systemic embolism, regardless of whether the subject is receiving treatment at the time of the event.

Secondary efficacy endpoints

The secondary efficacy endpoints will be time to first occurrence of confirmed:

- ischemic stroke or stroke of unspecified type
- hemorrhagic stroke
- systemic embolism
- all cause death
- composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding
- composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism and major bleeding in warfarin naive subjects
- composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, all cause death
- composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding, all cause death
- composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, myocardial infarction, all cause death.

Primary safety endpoint

The primary safety endpoint will be time to first occurrence of confirmed major bleeding during the treatment period.

Secondary safety endpoint

The secondary safety outcome for this trial is a composite of confirmed major bleeding and confirmed clinically relevant non-major bleeding. Other safety outcome measures will also be assessed, and will include minor bleeds, fractures and other AEs as well as abnormal standard clinical laboratory test results.

Bleedings

Major bleeding is defined as bleeding that is clinically overt and that satisfies one of the following criteria 1) bleeding resulting in a decrease in hemoglobin of 2 g/dL or more over a 24-hour period; 2) bleeding leading to a transfusion of 2 or more units of packed red blood cells; 3) bleeding that occurs in a critical site (intracranial intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal); or 4) bleeding that leads to death.

Clinically relevant non-major bleeding is defined as a bleeding event that is clinically overt, that satisfies none of the additional criteria required for the event to be adjudicated as a major bleeding event, that leads to either 1) hospital admission for bleeding or 2) physician guided medical or surgical treatment fo bleeding or 3) a change in antithrombotic therapy.

Minor bleeding All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding will be classified as minor bleeding.

Fatal bleeding is defined as a bleeding event that the CEC determines is the primary cause of death or contributes directly to death.

Statistical Methods

Sample Size Estimation: A key aspect of developing the adequate sample size for this trial is arriving at the appropriate non-inferiority margin. Warfarin has been studied in 6 different placebo controlled randomized trials in subjects with AF. There is a meta-analysis for these studies.

The relative risk reduction 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 (ie, control compared with warfarin) is 1.88 (1/0.53).To establish that at least half of the warfarin effect is preserved, the noninferiority margin is 1.88 or 1.38 (ie, 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) Using the meta-analysis for these 6 studies is showed that the events/patient-year for warfarin is 2.38 %. So, the events/patient-year for apixaban is 1.38 * 2.38 = 3.28%.

It is set that the duration of the study is 2.3 years. From the literature it is known that the number of the strokes is 1.2 / 100 patient-year.

As a result the sample size for power 90% , p-value 5% and Δ= 3.28-2.38=0.9% is 7,130 for each treatment.

After the sample size estimation in each treatment, add additional 10%

Thus, the sample size is 7843 for each treatment. Overall n=7843*2=15.686

Efficacy & Safety Analysis

Efficacy Analysis: The primary efficacy endpoint will be the time to first occurrence of confirmed stroke (ischemic, hemorrhagic, or of unspecified type), or systemic embolism during the study, regardless of whether the subject is receiving treatment at the time of the event. The primary objective is to determine if apixaban is non-inferior to warfarin for the primary efficacy endpoint. To conclude non-inferiority it will be necessary to demonstrate that the apixaban event rate for the primary endpoint is not materially higher than the warfarin event rate as measured by the relative risk of apixaban relative to warfarin.Tests using each non-inferiority margin will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by prior warfarin / VKA status (experienced, naïve).
For the regulatory claims associated with the primary and the key secondary objectives listed, the following hierarchical testing procedure will be used:

Non-inferiority for the primary efficacy endpoint will be assessed first. If non-inferiority (using a non-inferiority margin of 1.38) is demonstrated then:

I.superiority for the primary efficacy endpoint will be tested
II. if superiority for the primary efficacy endpoint is
-not demonstrated, then stop
-demonstrated, then non-inferiority for major bleeding will be tested
III.if non-inferiority for major bleeding is
- not demonstrated, then stop
- demonstrated, then superiority for all cause death will be tested.

Safety Analysis: The primary safety endpoint will be time to first occurrence of major bleeding during the treatment period. A point estimate and two-sided 95% CI for relative risk and a p-value for the test of equality of rates (RR = 1) will be calculated. The test will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by prior warfarin status (experienced, naïve). Kaplan- Meier methodology will be used to estimate event rates over time. Subjects without events during the treatment period will be censored. The incidence of confirmed major bleeding events, confirmed clinically relevant non-major bleeding events, minor bleeding events and all bleeding AEs occurring through the end of the treatment period will be summarized by treatment group.

TABLE OF CONTENTS

UNIT 1 : Introduction

This unit is refered to the definition of atrial fibrillation, the reasons why are needed to find a new drug called Apixaban in order to face this heart disorder and finally will be given information about this new medicine. In addition to that, earlier studies Phase I and Phase II are reported in order to determin the dose of the drug and record the adverse events.

1.1 Atrial fibrillation

Atrial fibrillation (AF) is the most common chronic arrhythmia globally. In the United States the prevalence of AF is 0.9%, or about 2.3 million persons, but this increases with advancing age, with over 10% percent of persons aged 80 or older affected. The prevalence of the disease is expected to double in the next 25 years as the population continues to age; the life time risk of developing AF is 1 in 4 for adults 40 years of age or older. Patients with AF suffer from a number of medical complications, but chief among these is stroke. AF leads to the formation of thrombus in the fibrillating left atrium, which can then embolize into the systemic circulation resulting in stroke or systemic embolization. AF is a major cause of stroke and is responsible for 15 - 20% of all strokes. In persons over the age of 80, AF is the leading cause of stroke, and such strokes are particularly devastating in the elderly, where they are a major cause of both morbidity and mortality.

In the past 20 years, there have been significant advances in our understanding of AF, its causes, treatment and complications. Although new antiarrhythmic drugs and ablation techniques have been introduced, a mainstay of therapy for AF at present is anticoagulation with warfarin or other vitamin K antagonists (VKAs) to prevent stroke and systemic embolism. The VKAs, of which warfarin is the most common example, have been in use for over 50 years. All of these compounds exert their anticoagulant effect by antagonizing the vitamin K dependent epoxidation cycle; all are monitored by means of the international normalized ratio (INR).
Warfarin has been demonstrated to be effective in reducing the risk of stroke in subjects with AF, with an impressive relative risk reduction (RRR) of 62% (95% CI, 48% to 72%) when compared to placebo.

1.2 The reasons why a new drug is demanded

Despite this acknowledged efficacy, warfarin and other VKAs suffer from a number of liabilities. The therapeutic range of VKAs is narrow, and dosing can be unpredictable due to genetic and environmental factors. Food effects and interactions with numerous prescription, non-prescription and botanical products are known and the need for therapeutic monitoring is a barrier to effective therapy with VKAs. Lack of maintenance **o**f the INR in the desired range can result in bleeding and the risk of intracranial hemorrhage appears to increase in the elderly, who paradoxically may benefit most from warfarin's effects to prevent ischemic stroke. Warfarin is a leading cause of adverse drug events and in a number of studies done world-wide, nearly half of those who might benefit from warfarin are not presently treated with the drug, 20% because they refuse to take it. Among those being treated with warfarin and other VKAs in well managed clinical trials, the INR is in the therapeutic range (2.0-3.0) ~60% of the time. Finally, studies reveal that in daily clinical practice warfarin is prescribed appropriately less frequently and its anticoagulation effects managed less well than the admittedly modest levels attained in clinical trials. In addition, recent studies have raised some concerns regarding the effects of VKAs on bone metabolism. Prospective data regarding increased incidence of fractures in at risk subjects on VKA are lacking from randomized trials. Such prospectively collected data is desirable.

These factors indicate that large numbers of subjects with AF and additional risk factors for stroke are either not being offered treatment with warfarin or refuse treatment with this agent. Those who are being treated with warfarin are often not protected from stroke whenever their INR falls below the therapeutic range, or controversy, may be at significantly increased risk for intracerebral hemorrhage should their INR climb to a supratherapeutic level. These limitations indicate a significant unmet need for effective stroke prevention in subjects with AF that cannot be addressed with warfarin therapy.

The development of a newer anticoagulation agent that is free of warfarin's liabilities is thus desirable. Such an agent should be oral, free from food effect and with fewer drug interactions than warfarin, but should have comparable efficacy in preventing stroke in AF subjects. Furthermore, this new agent should have well behaved, predictable pharmacokinetics with a low toxicity profile that would make it simple to dose. Lastly, it should have a wider therapeutic index and not require therapeutic monitoring.

1.3 Information about the new drug

Bristol-Myers Squibb (BMS) has developed a new drug called apixaban as an antithrombotic for subjects with AF who are at risk for stroke. Apixaban is a novel, selective, orally active inhibitor of the coagulation factor Xa (Fxa). FXa occupies a pivotal role in the clotting cascade, converting prothrombin to thrombin. Inhibition of FXa exerts anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin (Factor IIa), there by diminishing fibrin formation and platelet activation. While apixaban is a direct, orally available, reversible inhibitor of FXa, other agents act upon FXa by an indirect, anti-thrombin (AT) III mediated mechanism. Low molecular weight heparins (including enoxaparin) have relatively more effect on inhibiting FXa than IIa compared to unfractionated heparin. The pentasaccharide fondaparinux acts through AT III to specifically inhibit Fxa. Given the established utility of FXa inhibition in prevention and treatment of venous and arterial thrombotic disease, an orally available agent would be desirable.

1.4 Studies Phase I and Phase II

Apixaban has undergone considerable in vitro and in vivo study in a wide variety of preclinical models. BMS has initiated a broad program of preclinical and clinical research to evaluate the safety and effectiveness of apixaban in the prevention and treatment of VTE and ACS, and to prevent stroke in subjects with nonvalvular atrial fibrillation (AF) who have additional risk factor(s) for stroke.

Extensive Phase 1 testing revealed apixaban to have dose-proportional exposure up to 10 mg with a bioavailability of ~51 - 85% and a small volume of distribution (16 - 25 L). There is no food effect on apixaban absorption following the consumption of a high fat, high calorie meal, and pH is unlikely to exert an effect. Approximately 87% of the drug is protein bound in human serum. Apixaban has multiple pathways of elimination of which about 25% is renal and 75% is nonrenal, with an effective half-life of 10 - 15 hours. Metabolism is primarily by CYP3A4 and SULT1A1. Ketoconazole administration increases apixaban AUC by a factor of 2. The major circulating metabolite of apixaban (M1) is an inactive phenol sulfate conjugate. Apixaban and M1 have a low likelihood of prolonging QTc. Increases in anti-Xa activity closely track the apixaban concentration.
Apixaban was well tolerated when administered orally to rats (up to 600 mg/kg/day for 6 months) and to dogs (up to 100 mg/kg/day for 12 months). The animal to human exposure multiple (AUC) at the NOAEL for these studies corresponds to 17x and 59x in rats and dogs, respectively, relative to a clinical dose of 5 mg BID. No significant toxicology findings were noted in animals during exposure, nor in subsequently in those euthanized for histopathologic examination.

In Phase 1 studies completed as of September 2006, there have been no serious adverse events (SAEs) or major bleeding events; the majority of bleeding-related adverse events (AEs) were considered mild in intensity by the Investigator and required little (e.g., application of a compress) or no treatment.

Also, BMS has completed a Phase 2 VTE prevention study (CV185010) in subjects undergoing total knee replacement surgery. In this trial, all doses of apixaban had lower rates of VTE than either enoxaparin and warfarin, with an acceptable bleeding profile.There were relatively few reports of adjudicated major bleeding events in the Phase 2 DVT prevention study (CV185010). Major bleeding occurred at a low rate in the apixaban arms (0-3.3%) and at a rate of 2.6% in the 5 mg BID dosing arm. No major bleeding events were noted in the enoxaparin or warfarin arms. In similar published studies, major bleeding events occur in 1-2% of enoxaparin treated subjects and < 1% of warfarin treated subjects. Total bleeding occurred at a rate of 6.5% in the 5 mg BID dosing arm of apixaban, compared with 5.4% in the enoxaparin arm and 5.3% in the warfarin arm.

UNIT 2 : Study Objectives

2.1 Primary Objective

To determine if apixaban is noninferior to warfarin (INR target range 2.0-3.0) in the combined endpoint of stroke (hemorrhagic, ischemic or of unspecified type) and systemic embolism, in subjects with AF and at least one additional risk factor for stroke.

2.2 Secondary Objectives

- Key Secondary Objectives

The key secondary objectives are to determine, in subjects with AF and at least one additional risk factor for stroke (5.4.1), if apixaban is superior to warfarin (INR target range 2.0 – 3.0) for the combined endpoint of stroke (hemorrhagic, ischemic or of unspecified type) and systemic embolism, major bleeding (ISTH) and all-cause death.

- Other Secondary Objectives

To compare, in subjects with AF and at least one additional risk factor for stroke, apixaban and warfarin with respect to the composite endpoint of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism and major bleeding, in warfarin naive subjects, the composite endpoint of stroke, (ischemic, hemorrhagic or of unspecified type), systemic embolism and major bleeding, the composite endpoint of stroke (ischemic, hemorrhagic or of unspecified type), systemic embolism and all cause death, the composite endpoint of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding and all cause death and the composite endpoint of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, myocardial infarction and all cause death.

To assess the safety of apixaban in subjects with AF and at least one additional risk factor for stroke.

UNIT 3 : Ethical Considerations

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive. Furthermore, the study will be conducted in compliance with the protocol. The protocol, the amendments of protocol and the subject informed consent will receive IRB/IEC approval opinion prior to initiation of the study.

3.2 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, prior to clinical trial study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study trial.

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, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation in or to be withdrawn from, the clinical study at any time should be considered by the Investigator.

In order to successfully maintain the safety objectives of this endpoint driven trial, it is necessary that each subject's follow-up and vital status be maintained through to the end of the study. All reasonable efforts must be made to locate subjects to determine and report their current and ongoing status.The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

UNIT 4 : Investigation Plan

4.1 Study Design and Duration

This study is designed to evaluate the efficacy and safety of apixaban compared to warfarin (INR target range 2.0 - 3.0), a drug approved and widely employed for the prevention of stroke and systemic embolism in subjects with nonvalvular atrial fibrillation with additional risk factor(s) for stroke. The primary endpoint, a composite of stroke (ischemic, hemorrhagic, or of unspecified type) and systemic embolism will be tested using a noninferiority approach. The trial will be event driven thus the number of subjects required and length of treatment are best estimates based on event rates in similar trials. The expected duration of the study, from first subject, first visit through the last follow-up phone contact for the last subject, is approximately 60 months, but the final duration per subject will be determined by the time required to accrue 433 primary efficacy events. All subjects will be followed from randomization until the study end date.

Eligible subjects will be randomized in a 1:1 ratio to either apixaban or warfarin. Each arm will contain ~7.843 subjects (for a total of ~15.686 randomized subjects). Subjects with AF and at least one additional risk factor for stroke will be evaluated for study eligibility. Emphasis will be placed on recruiting both warfarin naïve and warfarin experienced subjects into the trial The study will be double-blind, double-dummy, with titration based on central monitoring of INR measurements utilizing encrypted point of care (POC) devices, centralized dosing recommendations, and sham apixaban titration. Subjects will receive active apixaban tablets and placebo warfarin tablets or placebo apixaban tablets and active warfarin tablets.

INR testing frequency will occur at least every month during the treatment period, more frequently during titration and if clinically indicated. Each subject will return to have a blood sample drawn and processed in a POC device. The device will deliver an encrypted result to the Investigator who will telephone or electronically transmit the result. This facility will process the information in a blinded manner and return either a true INR value (in the case of a subject receiving warfarin) or a sham INR value (in the case of a subject receiving apixaban), along with a dosage recommendation. The final dosing decision will rest with the Investigator.

At the INR visits, only INR monitoring with POC device, assessment of outcomes, and assessment of study medication compliance will be performed. In addition, at the quarterly visits during the treatment period (Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57) assessment of changes in concomitant medication, vital signs and laboratory assessments will be performed and at the yearly visits during the treatment period (Months 12, 24, 36, and 48) physical measurements and a 12 lead ECG will be obtained, and electrocardiograms will be performed. All subjects will be followed for the development of stroke (hemorrhagic, ischemic or unspecified), systemic embolism, myocardial infarction, death, bleeding, hospitalization or treatment discontinuation until the end of the study. Follow-up of subjects who discontinued study drug prior to the attainment of 433 primary events in the study should occur quarterly by a telephone call: the final follow-up visit should be in-person, if at all possible, and should be performed within approximately 30 days after the attainment of 433 primary efficacy events in the study.

SAEs (that occurred within 30 days after the last study dose of double-blind study drug) and study outcomes will be documented at all follow-up contacts.

There are three study periods expected to last up to of 60 months in duration:
(1) a screening period of up to 14 days, (2) a treatment period lasting until the earlier of a subject's treatment

discontinuation and the attainment of 433 primary efficacy events and (3) a follow-up period lasting until the latter of 30 days after treatment discontinuation or the attainment of 433 primary efficacy events.

Expected duration of the study, from first subject first visit through last subject, last visit is approximately 60 months.

4.1.1 Executive Committee

An academic Executive Committee (EC) participated in the development of the protocol and will provide ongoing scientific and operational oversight to the study. The Executive Committee will provide suggestions for potential investigators and National Coordinators, will monitor progress of study enrollment, make recommendations to the sponsor based on the DMC recommendations and oversee the presentation and publication of the trial results. The Executive Committee will include clinical experts representing the specialties involved in management of subjects with atrial fibrillation (cardiology, neurology, electrophysiology, coagulation and thrombosis, or hypertension) and experienced in large clinical trial methodologies.

4.1.2 Clinical Events Committee

The Clinical Events 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 and they will consider the impressions of the Investigator. Their decisions will be used for the final statistical analyses.

4.1.3 Data Monitoring Committee

This study will be conducted under the auspices on an independent Data Monitoring Committee (DMC), whose membership and activities are described in the DMC charter. The DMC will 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 (treatment x vs. treatment y) 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. The DMC may recommend early termination of the trial, for safety reasons.

4.2 Study Population

4.2.1 *Inclusion Criteria*

For entry into the study, the following criteria MUST be met.

- Age ≥ 18 years
- In atrial fibrillation or atrial flutter not due to a reversible cause and documented by ECG (electrocardiogram) at the time of enrollment.

Or

If not in atrial fibrillation/flutter at the time of enrollment, must have atrial fibrillation/flutter documented on two separate occasions, not due to a reversible cause at least 2 weeks apart in the 12 months prior to enrollment. Atrial fibrillation/flutter may be documented by ECG, or as an episode lasting at least one minute on a rhythm strip, Holter recording, or intracardiac electrogram (from an implanted pacemaker or defibrillator).

- One or more of the following risk factor(s) for stroke:

1) Age 75 years or older
2) Prior stroke, transient ischemic attack or systemic embolus
3) Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with an LV ejection fraction (LVEF) ≤ 40% by echocardiography, radionuclide study or contrast angiography
4) Diabetes mellitus
5) Hypertension requiring pharmacological treatment

- Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the treatment period of the study or for 2 weeks after the last dose of study medication,

whichever is longer, in such a manner that the risk of pregnancy is minimized.

- All subjects must provide signed written informed consent

4.2.2 *Exclusion Criteria*

- Atrial fibrillation or flutter due to reversible causes (e.g. thyrotoxicosis, pericarditis)
- Moderate or severe mitral stenosis
- Conditions other than atrial fibrillation that require chronic anticoagulation (e.g. prosthetic mechanical heart valve)
- Recent ischemic stroke (within 7 days)
- Increased bleeding risk that is believed to be a contraindication to oral anticoagulation (e.g. previous intracranial hemorrhage)
- Planned major surgery
- Planned atrial fibrillation or flutter ablation procedure
- Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, or diastolic BP > 100 mm Hg)
- Active infective endocarditis
- Severe comorbid condition with life expectancy of ≤ 1 year
- Use of an unapproved, investigational drug or device within the past 30 days
- A need for aspirin at dose of > 165 mg a day or for both aspirin and clopidogrel
- Severe renal insufficiency (serum creatinine > 2.5 mg/dL or a calculated creatinine clearance < 25 mL/min
- Subjects with active liver disease or persistent elevation of liver enzymes/bilirubin:

ALT or AST ≥ 2 times the ULN, TBL ≥ 1.5 times the ULN and ALP ≥ 2 times the ULN

- Active alcohol or drug abuse, or psychosocial reasons that make study participation impractical

4.2.3 *Discontinuation of Subjects from Treatment*

Subjects should discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- If ALT ≥ 5 x ULN on any two consecutive occasions
- Total bilirubin ≥ 2.0 x ULN on any two consecutive occasions
- Pregnancy
- Termination of the study by BMS

UNIT 5 : Treatments

5.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketed authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

In this protocol, investigational product(s) is/are:

Apixaban 5 mg and 2.5 mg tablets and matching apixaban-placebo tablets
Warfarin 2 mg tablets and matching warfarin-placebo tablets

5.2 Identification

The following investigational products will be provided by Bristol-Myers Squibb, Pharmaceutical Research Institute:

Product	Potency	Appearance
Apixaban (BMS-562247) film	5 mg	Reddish brown, plain, oval shaped, shallow
coated tablets		biconvex film coated tablet
Apixaban (BMS-562247) film	2.5 mg	Reddish brown, plain, oval shaped, shallow
coated tablets		biconvex film coated tablet
Placebo for apixaban	-	Reddish brown, plain, oval shaped, shallow
(BMS-562247) film coated tablets		biconvex film coated tablet
Warfarin Sodium (BMS-565793)	2 mg	Lavender, round, biconvex tablet with one face
tablets		bisected and the other face plain
Placebo for Warfarin Sodium	-	Lavender, round, biconvex tablet with one face
(BMS-565793) tablets		bisected and the other face plain

5.3 Randomization

Eligible subjects will be randomized in a 1:1 ratio to either apixaban or warfarin titrated to a target INR range 2.0 to 3.0. Subjects who are on warfarin or another Vitamin K antagonist (VKA) will have their VKA discontinued prior to randomization. Each arm will contain ~7.843 subjects. The randomization will be stratified by investigative site and prior warfarin/VKA status (experienced, naïve). Subjects will be classified as warfarin naïve if they have not previously received warfarin or another VKA or have received ≤ 30 consecutive days of treatment with warfarin or another VKA in the past. Otherwise the subject will be classified as warfarin experienced.

Randomization will be stratified according to whether patients had received warfarin previously and according to clinical site. Apixaban or matching placebo will be administered twice daily, with apixaban given in 5-mg doses or 2.5-mg doses will be used in a subset of patients with two or more of the following criteria (5.4.1) : an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg per deciliter or more. Warfarin (or matching placebo) will be provided as 2-mg tablets and will be adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0. Patients who were receiving a vitamin K antagonist before randomization will be instructed to discontinue the drug 3 days before randomization, and the study drug will be initiated when the INR was less than 2.0. INRs will be monitored with the use of a blinded, encrypted, point-of-care INR device. An algorithm was provided to guide the adjustment of the warfarin dose. The time that patients' INRs will be within the therapeutic range will be

calculated by the Rosendaal method.These data will be reported back to the participating centers with advice for optimal INR control.

At the time of enrollment, each subject will be assigned a unique sequential subject number by the IVRS-Interactive Voice Response System. 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 a 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. Each subject who meets the inclusion/exclusion criteria will be randomly assigned to one of two treatment groups: apixaban or warfarin adjusted to a target INR (range 2.0 - 3.0).

5.4 Selection and Timing of Dose for Each Subject

Subjects who are on warfarin or another VKA prior to randomization will have their VKA discontinued or the dose reduced prior to randomization and will not be dosed with study drugs until the INR is < 2.0. Subjects will receive either apixaban (and warfarin-placebo) or warfarin (and apixaban-placebo) following randomization during a titration phase. Warfarin initiation will avoid loading doses and will be based on several clinical factors. In subjects who are warfarin experienced with adequate INR control, resumption of their previous dosing will generally be the best option.

In subjects who are either warfarin naïve or whose previous dosing history or INR control is not available, age may be the most useful criterion to determine warfarin starting dose. In subjects < 80 years of age, initiation with a daily dose of up to 6 mg of warfarin followed by INR testing on Day 3 or 4 is recommended. In subjects ≥ 80 years of age, initiation with a daily dose of up to 4 mg of warfarin followed by INR testing on Day 3 or 4 should be considered. Subsequent warfarin doses will be recommended based upon an algorithm, the final decision on dosing will rest with the Investigator. INR monitoring will begin on the third or fourth day following initiation of study drug administration and will be performed twice a week for two weeks, once a week for two weeks, and monthly thereafter once a stable INR is attained. An Investigator may increase the frequency of INR monitoring if it is considered clinically indicated.

5.4.1 Dose Modifications

For certain subjects who may be deemed to be at higher risk of bleeding with study drug (e.g. the elderly, small stature, renal impairment), a lower dose of apixaban (2.5 mg BID) will be used. Subjects who fulfill any two of the following criteria will have their apixaban dose reduced to 2.5 mg BID at the time of randomization only:

I Age ≥ 80 years
II Body weight ≤ 60 kg
III Serum creatinine ≥ 1.5 mg/dL

5.5 Blinding

This study will be conducted in a blinded fashion. To maintain blinding of study treatment, study medications will be prepared in a double-dummy design using placebo matching the active treatments. Subjects, Investigators, members of any of the administrative and adjudicating committees, and the Sponsor's staff conducting the study, will not have access to individual subject treatment assignments. The Randomization Center at BMS will have access to such assignments.

5.5.1 Procedure of Blinding

Treatment will be randomized to either adjusted-dose warfarin, target international normalized ratio (INR) 2.0 to 3.0, or fixed-dose apixaban, 5 or 2.5 mg twice daily. Using a double-dummy design to maintain blinding, all patients will receive both assigned anticoagulant and placebo and will be undergo blood sampling at intervals of 30 days or fewer. INR measurements will be by finger-stick sampling using uniform point-of-care devices.

INR testing frequency will occur at least every month during the treatment period, more frequently during titration and if clinically indicated. Each subject will return to have a blood sample drawn and processed in a POC device. The device will deliver an encrypted result to the Investigator who will telephone or electronically transmit the result along with the subject's identification number, date and time to a central response facility. This facility will process the information in a blinded manner and return either a true INR value (in the case of a subject receiving warfarin) or a

sham INR value (in the case of a subject receiving apixaban), along with a dosage recommendation. The final dosing decision will rest with the Investigator.

5.5.2 Unblinding

Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician. Before, breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without unblinding.

When knowledge of the subject's randomized treatment assignment would have a meaningful impact on individual management, for example in many cases of clinically significant bleeding or the need for urgent invasive procedures, the subject's treatment assignment should be unblinded. This information should be provided to those who are caring for the subject and as few other people as possible. In these cases, we will minimize bias by assuring that the clinical events committee remains blinded to treatment assignment, even if the investigator has been unblinded. The need to break the blind must first be discussed with the responsible Medical Monitor.

5.5.3 Invasive Procedures and Surgery

Several factors govern the management of anticoagulation in this study with respect to surgery and invasive procedures as well as the management of bleeding that may occur in subjects on study drugs.
These are:
• The risk of thromboembolism in an individual subject (low, intermediate or high)
• The risk of bleeding associated with the procedure or surgery
• Whether the surgery or invasive procedure is elective or emergent in nature
• The desirability of maintaining blinding, if at all possible, without creating risk for the subject
• The different times of onset and offset of anticoagulant effect for warfarin and apixaban (warfarin needs to be discontinued earlier than apixaban to permit its effects to abate, and needs to be started in advance of apixaban to achieve a stable anticoagulant effect)

5.5.3.1 *Elective Procedures*

In general, local standards of care for discontinuation of anticoagulation prior to elective procedures/surgery should be employed. These are summarized below based upon the risk of thromboembolism:

High risk of thromboembolism

- Stop warfarin/warfarin-placebo 4 days before the planned procedure.

- Monitor the INR using the encrypted POC device as necessary.

- Begin full dose UFH or LMWH as the INR falls (approximately 2 days before the planned procedure). The doses employed should conform to the local standard of care. Stop apixaban/apixaban-placebo.

- Once the POC INR has attained a value deemed appropriate for the proposed procedure, this value may be confirmed by locally obtained coagulation studies (e.g. INR, PT, aPTT) conforming to the site's standard of care.

- Maintain on UFH or LMWH in the postoperative period as per the local standard of care (full dose preferred) until INR is therapeutic.

- Restart warfarin/warfarin-placebo (usually the night of the day of surgery) and apixaban/apixaban-placebo postoperatively (when the INR is therapeutic) when it is deemed safe to do so. Stop UFH/LMWH.

5.5.3.2 *Emergency Procedures*

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 apixaban) and unblinding may be necessary. Regardless of treatment, study drugs should be discontinued and standard laboratory coagulation tests (PT/INR, aPTT, platelet count, etc.) performed. The procedure should be carried out and in such a way to minimize the risk of bleeding.

Subjects receiving warfarin should be managed according to the local standard of care. The anticoagulant effects of warfarin will be reflected in the PT and INR and, after discontinuation, will take several days (3 - 5) to return to normal. Warfarin can be reversed more quickly by giving oral or intravenous vitamin K (depending on circumstances and the local standard of care) and/or with fresh frozen plasma (FFP). Furthermore, for subjects receiving apixaban, the risk of bleeding with invasive procedures is unknown. At therapeutic doses, the anticoagulant effects of apixaban will not be reflected in standard coagulation tests; there is no reversal agent for apixaban. Vitamin K and protamine sulfate are not expected to affect the anticoagulant effect of apixaban, and may carry some risk.

5.6 Concomitant Treatments

5.6.1 Prohibited and/or Restricted Treatments

The following medications or therapies are prohibited:

• Potent inhibitors of CYP3A4 (e.g., azole antifungals [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir], and nefazadone)
• Aspirin > 165 mg/day
• Other antithrombotic agents (e.g., UFH, LMWH, direct thrombin inhibitors, fondaparinux) [Note: UFH and LMWH may be used as part of a bridging strategy, see Section 5.4.1.3 Bridging Strategy.]
• GP IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)

If treatment with an agent above becomes necessary, study drug should be temporarily interrupted, and restarted as soon as possible following discontinuation of the prohibited medication or therapy.

Restricted agents:

The administration of the following agents in subjects on study drug should be done cautiously given the increased risk of bleeding. In such cases, consideration of interruption of the study drug may be warranted; this decision should be made after a careful assessment of the risks and potential benefits.

• Concomitant (simultaneous) use of both aspirin (≤ 165 mg/day) and a thienopyridine (e.g., clopidogrel, ticlopidine)
• Chronic (> 3 months) daily NSAIDs
• Cytotoxic/myelosuppressive therapy

UNIT 6 : Study Assessments & Procedures

6.1 Procedures by Visit

The study is divided into 3 periods as follows:

-Screening period
Screening period of up to 14 days. Subjects who enter the study on warfarin or a VKA may continue in the screening period longer than 14 days until their INR is < 2.0 and they are eligible to be randomized.

-Treatment Period
Lasting until the earlier of a subject's treatment discontinuation or the attainment of 433 primary efficacy events.

-Follow-up Period
Lasting until the latter of 30 days after treatment discontinuation or the attainment of 433 primary efficacy events.

6.1.1 Screening Period

The Investigator will:
• Obtain written informed consent
• Obtain relevant medical history, including history of fractures
• Perform physical examination
• Obtain vital signs
• Obtain physical measurements including height, weight, and hip and waist circumference
• Obtain 12-lead ECG
• Obtain clinical laboratory tests (including INR, preferably from central lab)
• Obtain urine pregnancy test
• Determine if subject meets inclusion/exclusion criteria
• Assess concomitant medication use (within 30 days prior to screening visit)
• Assess previous warfarin/VKA experience

6.1.2 Treatment Period

6.1.2.1 Day 1

After randomization, the Investigator will:
• Administer study drug
• Assess for AEs
• Assess changes in concomitant medication use
• Assess for outcomes (death, stroke, systemic embolism, myocardial infarction, bleeding)

6.1.2.2 All Monthly Visits and INR Visits

INR monitoring will begin on the 4th day following initiation of drug administration and will be performed twice a week for two weeks, once a week for two weeks (i.e. Day 4, Week 1, Day 10, Week 2, Week 3, Week 4), and monthly thereafter once a stable INR is obtained, unless the subject is no longer taking IP. INR measurements are to be reinstated if a subject recommences IP as above. Each subject will return to have a blood sample drawn and processed using the POC device. The device will deliver an encrypted result to the Investigator who will telephone or electronically transmit the result along with the subject's identification number, date and time, to a central response facility. This facility will process the information in a blinded manner and return either a true INR (in the case of a subject receiving warfarin) or a sham INR value (in the case of a subject receiving apixaban), along with a dosage recommendation. The final dosing decision will rest with the Investigator. The POC device may be used prior to randomization to determine if the INR value is < 2.

At the INR visits the Investigator will:

• Perform POC testing for INR

• Obtain laboratory tests for assessment of LFT and CK (at Months 1 and 2 visits only)

• Obtain urine pregnancy test (at all monthly visits)

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

• Assess changes in concomitant medication use (at Month 1 visit only)

• Assess for AEs

• Collect Study Medication

• Assess Study Medication use

• Dispense Study Medication

6.1.2.3 Final Treatment Visit

The Investigator will:

• Obtain 12 Lead ECG (within two months prior to FTV)

• Obtain vital signs

• Obtain clinical laboratory tests including Hematology panel, Chem 21 panel, and urinalysis (within two months prior to FTV)

• Obtain urine pregnancy test

• Assess for fractures (within two months prior to FTV)

• Assess for AEs

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

• Assess changes in concomitant medication use

• Collect Study Medication (blinded apixaban may be redispensed to perform bridging and then collected after the last dose is administered, blinded warfarin should be collected at the FTV).

• Assess for Study Medication use

6.1.2 Follow-up Period

Subjects will be followed-up until the later of either 30 days after the last dose with double-blind study drug or the attainment of 433 primary efficacy events. Subjects who discontinued study drug prior to the EOTP date should have a phone call quarterly and if possible a final visit in-person should be performed anytime within approximately 30 days after the attainment of 433 primary efficacy events (EOTP date) but no sooner than 3 weeks after the last dose of double-blind study drug. Subjects who completed the FTV should have a telephone contact approximately 30 days after FTV.

At all follow-up contacts the Investigator or designee will:

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

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

6.2 Safety Assessments

6.2.1 Bleeding Assessment

Acute clinically overt bleeding is defined as new onset, visible bleeding or signs or symptoms suggestive of bleeding with confirmatory imaging techniques which can detect the presence of blood (e.g., US, CT, MRI).

The definition of major bleeding described below is adapted from the International Society on Thrombosis and Hemostasis (ISTH) definition

Major bleeding event **is defined as a bleeding event that is:**

• Acute clinically overt bleeding accompanied by one or more of the following:
− A decrease in hemoglobin (Hgb) of 2 g/dL or more over a 24-hour period
− A transfusion of 2 or more units of packed red blood cells
− Bleeding that occurs in at least one of the following critical sites:
♦ Intracranial
♦ Intra-spinal
♦ Intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)

♦ Pericardial
♦ Intra-articular
♦ Intramuscular with compartment syndrome
♦ Retroperitoneal.

• Bleeding that is fatal.

Clinically relevant non-major bleeding event: **The definition of clinical relevant** non-major bleeding will be acute or sub-acute clinically overt bleeding that does not satisfy the criteria for major bleeding and that leads to either 1) hospital admission for bleeding or 2) physician guided medical or surgical treatment for bleeding or 3) a change in antithrombotic therapy.

Minor bleeding events: All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant non-major bleeding will be classified as minor bleeding.

Fatal bleeding event is defined as a bleeding event that the CEC determines is the primary cause of death or contributes directly to death. All acute clinically overt bleeding events will be adjudicated by the CEC as a major bleeding event, or clinically relevant non-major bleeding event. Minor bleeding events will not be adjudicated.

6.2.1.1 Treatment Guidelines for Bleeding/Suspected Bleeding

Subjects with bleeding or suspected bleeding will undergo confirmatory laboratory or other testing (e.g., US, CT, MRI) and a (S)AE CRF must be completed. The date and time of the onset of the bleeding event will be recorded on the CRF. Also, for subjects with bleeding, study drug may or may not be held at the discretion of the local physician and investigator. A risk / benefit determination should be made (as would be normally done with warfarin) weighing the subject's risk of further bleeding against the subject's risk of thromboembolism and benefit from continued anticoagulation. The bleeding should otherwise be managed according to local standard of care.

For subjects with clinically significant bleeding, the study drugs should generally be held. Bleeding should be managed according to local standard of care and may include measures such as:

- Local measures to stop the bleeding
- Volume resuscitation, and transfusion of blood products as appropriate
- Standard laboratory tests e.g. hemoglobin, hematocrit, PT/INR, aPTT, platelet count, etc. (recognizing that the anticoagulant effects of apixaban will not be reflected in standard coagulation tests)

6.2.2 Laboratory Assessments

Blood and urine samples will be obtained on selected visits (screening, quarterly visits, annual visits and at the end of treatment visit) for clinical laboratory evaluations. A central laboratory will perform the analysis and will provide reference ranges for these tests. The following laboratory tests are required for this study, and will be analyzed by a Central Laboratory:

Hematocrit, Hemoglobin, Red Blood Cell Count, MCV, White Blood Cell Count ,Lymphocytes, Platelet Count, Creatinine, ALP, ALT, AST, Direct Bilirubin and Total Bilirubin.

For the central laboratory assessments, materials and detailed instructions for specimen collection, processing, storage and shipment will be provided in special kits and will be described in a separate laboratory manual.

6.2.3 Pregnancy Tests

A pregnancy test to be conducted at the site:

• At screening

• On Day 1(if the screening pregnancy test is performed within 48 hours prior to first dosing of study medication, then the pregnancy test does not need to be repeated on Day 1)

- At all monthly visits
- At End of Treatment Visit

6.2.4 Creatinine Clearance

Based on the results of the enrollment visit clinical laboratory tests, the enrollment criterion for creatinine clearance will be estimated by the method of Cockcroft and Gault:
Clcr (mL/min) = [(140 - age) x (weight in kg) (x 0.85 for females)] / serum creatinine (mg/dL) x 72

6.3 Efficacy Assessments

6.3.1 Primary Efficacy Assessment

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. Stroke and systemic embolism are defined below and will be adjudicated by the CEC.

Stroke

Diagnosis of stroke will require the abrupt onset of focal neurological symptoms lasting at least 24 hours. It is strongly recommended (but not required) that an imaging procedure such as a CT scan or MRI be performed. All strokes will be classified as definite ischemic, definite hemorrhagic or type uncertain. A vascular imaging procedure such as a carotid ultrasound is recommended whenever possible (but not required) for subclassification of ischemic strokes into cardioembolic, lacunar or large artery. The level of disability and stroke severity will be assessed at presentation and at the next two regularly scheduled follow-up visits using the modified Rankin score.

Systemic Embolism

Systemic embolism will be judged to occur where there is a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries), which is supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing.

6.3.2 Secondary Efficacy Assessment

Secondary efficacy assessments will include assessments of combined efficacy and safety endpoints involving ischemic stroke, hemorrhagic stroke, stroke of unspecified type, systemic embolism, myocardial infarction, major bleeding and all cause death. The endpoints of death and non-fatal myocardial infarction (MI) are defined below and will be adjudicated by the CEC.

Death

Death will be defined as all-cause mortality. Deaths will be classified as either cardiovascular or non-cardiovascular. All deaths will be assumed to be cardiovascular in nature unless a non-cardiovascular cause can be clearly provided.

i) Cardiovascular
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).

ii) Non-cardiovascular
This category includes all deaths due to a clearly documented non-cardiovascular cause, such as respiratory failure (excluding cardiogenic pulmonary edema), hemorrhage (other than intracranial), infections/sepsis, neoplasm, and trauma (including suicide and homicide).

Myocardial Infarction

The following criteria satisfies 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.

UNIT 7 :Adverse Events

7.1 Definitions

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

7.1.1 Serious Adverse Events

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; it does not refer to an event which hypothetically might have caused death if it were more severe)
• requires inpatient hospitalization or causes prolongation of existing hospitalization
• results in persistent or significant disability/incapacity
• is a congenital anomaly/birth defect (note: reports of congenital anomalies/birth defects must also be reported on the Pregnancy Supplemental Form)
• is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

7.2 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more Aes.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all Aes: onset, duration, intensity, seriousness, relationship to investigational product, and action taken. The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with clinical study procedures. All SAEs must be collected which occur within 30 days of discontinuation of dosing with double-blind study drug. All SAEs must be followed until resolution. In addition, the Investigator should notify BMS of any SAE which may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page of the CRF and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the Investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page of the CRF. Moreover, if an ongoing SAE

changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. Supporting documentation such as hospital discharge summaries and autopsy reports should be forwarded to BMS in the same manner. All SAEs should be followed to resolution or stabilization.

7.3 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 8.2 for reporting details.)

UNIT 8 : Statistical Considerations

8.1 Sample Size Estimation

The primary efficacy endpoint will be the time to first occurrence of confirmed ischemic stroke, hemorrhagic stroke, stroke of unspecified type or systemic embolism, regardless of whether the subject is receiving treatment at the time of the event. The primary objective is to determine if apixaban is non-inferior to warfarin for the primary efficacy endpoint.

A key aspect of developing the adequate sample size for this trial is arriving at the appropriate non-inferiority margin. Warfarin has been studied in 6 different placebo controlled randomized trials in subjects with AF. There is a meta-analysis for these studies.

The relative risk reduction 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 (ie, control compared with warfarin) is 1.88 (1/0.53).To establish that at least half of the warfarin effect is preserved, the noninferiority margin is 1.88 or 1.38 (ie, 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)

Defining a treatment effect on the log scale seems arguably more sensible statistically and mathematically for one basic reason. Suppose that the risk ratio C/P is 0.53, which amounts to a 1-0.53=0,47 = 47% reduction of risk by the control relative to the placebo. But, by inversion, P/C = 1/0.53= 1.88 which amounts to a 88% increase by the placebo relative to the control. The 47% decrease is not equal to the opposite of the 88% increase. This awkward difference may cause difficulty in interpretation of a treatment effect. Defining a treatment effect on the log risk ratio scale will avoid the difficulty because $\log C/P = -\log P/C$ and thus the effect of C vs. P differs from the effect of P vs. C only by sign.

Using the meta-analysis for these 6 studies is showed that the events/patient-year for warfarin is 2.38 %. So, the events/patient-year for apixaban is 1.38 * 2.38 = 3.28%.

It is set that the duration of the study is 2.3 years. From the literature it is known that the number of the strokes is 1.2 / 100 patient-years.

As a result the sample size for power 90% , p-value 5% and Δ= 3.28-2.38=0.9% is

$$n \geq \left(\frac{p_1*(1-p_1)+p_2*(1-p_2)}{D^2}\right)*(1.96+1.28)^2$$

$$n \geq \left(\frac{0.0238*(1-0.0238)+0.0328*(1-0.0328)}{0.009^2}\right)*(1.96+1.28)^2$$

$$n \geq \frac{0.023+0.032}{0.000081}*(1.96+1.28)^2$$

$$n \geq \frac{0.055}{0.000081}*10.5$$

$$n \geq 7130$$

After the sample size estimation in each treatment, add additional 10%

Thus, the sample size is 7843 for each treatment. Overall n=7843*2=15.686

Determination of number of events :

15.686 subjects
So, at 2.3 years which is the duration of trial the patient years are 2,3*15.686=36.078 patient-years

It is known as is mentioned that there are 1,2 strokes at 100 patient-year
For the study need the number of events at 36.078 patient-year. So, the number of events is (1.2*36.078)/100=433

8.2 Endpoints Definitions

8.2.1 Safety Endpoints

- Primary Safety Endpoint

The primary safety endpoint will be time to first occurrence of confirmed major bleeding.

- Secondary Safety Endpoints

The secondary safety outcome for this trial is a composite of confirmed major bleeding and confirmed clinically significant non-major bleeding. Other safety outcome measures will also be assessed, and will include minor bleeds, fractures and other AEs as well as abnormal standard clinical laboratory test results. All major bleeding and clinically relevant non-major bleeding outcomes will be adjudicated by the CEC.

8.2.2 Efficacy Endpoints

- Primary Efficacy Endpoint

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

- Secondary Efficacy Endpoints

The secondary efficacy endpoints will be time to first occurrence of confirmed:

• ischemic stroke or stroke of unspecified type

• hemorrhagic stroke

• systemic embolism

• all cause death

• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding

• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, all cause death

• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding, all cause death

• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, myocardial infarction, all cause death

• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism and major bleeding in warfarin naive subjects

All efficacy outcomes will be adjudicated by the CEC.

8.3 Analysis

8.3.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), prior warfarin / VKA status (experienced, naïve), risk factor type, number of risk factors, smoking history, baseline medications, atrial fibrillation type and onset.

8.3.2 Efficacy and Safety Analysis

To begin with, all subjects should be included in the groups to which they will be randomly assigned. This is an "intention to treat" analysis. If the result is statistically significant then will be applied per protocol analysis which should have the same results in intention to treat analysis.

Efficacy Analysis

Primary Censoring Scheme for Efficacy Endpoints

Subjects who do not experience an efficacy endpoint event will be censored at the earlier of their death date (when death is not part of the endpoint), last contact date (for subjects who withdraw consent to be followed up or are lost to follow-up) or the efficacy cut-off date. For endpoints other than all-cause death, the last contact date will be the last date on which the efficacy endpoint can be assessed. For instance, if a subject is only followed for survival status after date X, then date X will be the last contact date in the censoring scheme. For the all-cause death endpoint, the latest date on or prior to the efficacy cut-off date at which survival status can be determined will be used either as the date associated with the endpoint (if the subject died) or the censoring date (if the subject was determined to be alive).

- Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of confirmed stroke (ischemic, hemorrhagic, or of unspecified type), or systemic embolism during the study, regardless of whether the subject is receiving treatment at the time of the event. The primary objective is to determine if apixaban is non-inferior to warfarin for the primary efficacy endpoint. To conclude non-inferiority it will be necessary to demonstrate that the apixaban event rate for the primary endpoint is not materially higher than the warfarin event rate as measured by the relative risk of apixaban relative to warfarin.
The non-inferiority margin is 1.88 or 1.38 (ie, 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)

Tests using each non-inferiority margin will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by prior warfarin / VKA status (experienced, naïve).

- Key Secondary Analysis

For the regulatory claims associated with the primary and the key secondary objectives listed, the following hierarchical testing procedure will be used:

Non-inferiority for the primary efficacy endpoint will be assessed first. If non-inferiority (using a non-inferiority margin of 1.38) is demonstrated then:

I. superiority for the primary efficacy endpoint will be tested

II. if superiority for the primary efficacy endpoint is
-not demonstrated, then stop
-demonstrated, then non-inferiority for major bleeding will be tested

III. if non-inferiority for major bleeding is
- not demonstrated, then stop
- demonstrated, then superiority for all cause death will be tested.

Safety Analysis

- Primary Safety Analysis

The primary safety endpoint will be time to first occurrence of major bleeding during the treatment period. A point estimate and two-sided 95% CI for relative risk and a p-value for the test of equality of rates (RR = 1) will be calculated. The test will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by prior warfarin status (experienced, naïve). Kaplan- Meier methodology will be used to estimate event rates over time. Subjects without events during the treatment period will be censored.

- 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 through the end of the treatment period will be summarized by treatment group.

The incidence of AEs and of marked abnormalities in clinical laboratory tests will be summarized by treatment group. All AEs that are serious or that result in discontinuation of study drug will be described in depth

8.4 Interim Analysis

A formal interim analysis will be performed once 50% of the primary efficacy endpoint events have been confirmed by the CEC. In addition to that, if the number of events will not be gathered an interim analysis will be performed at 2 years of study.The objective of this interim analysis is to determine whether apixaban is superior to warfarin for the primary efficacy endpoint. No interim testing for non inferiority will be performed. If at the interim analysis the observed RR for the primary efficacy endpoint is below the critical value then the DMC may recommend that the trial be terminated for superior efficacy of apixaban. The DMC may choose a less stringent boundary to terminate the study for harm and may alter the number and timing of interim analysis.

UNIT 9 : Administrative Section

9.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

9.2 Records Retention

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures,

or for the period specified by the sponsor, whichever is longer. The Investigator must contact BMS prior to destroying any records associated with the study. BMS will notify the Investigator when the study records are no longer needed. If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.1 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACS	acute coronary syndrome
AF	atrial fibrillation
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	anti-thrombin
BID	twice-daily
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
CRF	case report form
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
D/C	discontinuation
D-dimer	D fragment released by plasmin degradation of fibrin
Df	degree of freedom
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
ECG	electrocardiogram
EOT	End of treatment
F1.2	prothrombin fragment 1.2
FSH	follicle-stimulating hormone
FTV	Final treatment visit
FXa	Factor Xa
GCP	Good Clinical Practice

HCG	human chorionic gonadotropin
Hct	hematocrit
Hgb	hemoglobin
HRT	hormone replacement therapy
ICH	International Conference on Harmonization
IEC	International Ethics Committee
INR	international normalized ratio
IRB	institutional review board
IU	international units
IV	intravenous
IVRS	Interactive Voice Response System
LFT	liver function tests
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI magnetic	resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PO	by mouth
POC	point of care
PT	prothrombin time
QD	once-daily
RBC	red blood cell count
RR	relative risk
RRR	relative risk reduction
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SE	systemic embolism
SD	Switch Day
TIA	transient ischemic attack
UFH	unfractionated heparin
ULN	upper limit of normal
US	ultrasound
VKA	vitamin K antagonist
VTE	venous thromboembolism
WOCBP	women of childbearing potential

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