Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Clinical Protocol CV185030

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 Subjects with Nonvalvular Atrial Fibrillation

(ARISTOTLE: Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation)

Revised Protocol Number: 04
Incorporates Amendment 11

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This protocol contains information that is confidential and proprietary to
Bristol-Myers Squibb (BMS) and Pfizer, Inc.

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.
Amendment 11 04-Aug-2010 The purpose of this amendment of the protocol for CV185-030 is:
To provide clarity to the close-out procedures for the study
To provide recommendation for switching from blinded study drug to open label treatment
To clarify the reporting requirements for SAEs and SOEs
To clarify requirements for follow-up of patients that have discontinued study drug.
This revision applies to all enrolled subjects.

Administrative letter 08 02-Jul-2010 Each apixaban/placebo bottle will be labeled with a 3-panel, double-blind yellow label printed in black ink, (except for batch number OA58966 only where each apixaban/placebo bottle will be labeled with a 3-panel, double-blind white label printed in black ink).

Amendment 10 11-May-2010 The purpose of Amendment 10 for CV185030 is to address three major issues.

1) The first is to bring the objectives and associated statistical testing into alignment with guidance received from a health authorities. The latter have expressed concerns about a “net clinical benefit” endpoint that would combine, in a single composite endpoint, the primary efficacy endpoint with major bleeding; the concern is how to determine appropriate relative weights of such events and whether they can be combined into a net clinical benefit. Although the endpoint will still be assessed, the formal test of superiority associated with it has been deleted and has been replaced by superiority tests for each of its components, efficacy and bleeding, separately. There is also a lack of consensus in the statistical community, including within health authorities, as to whether the originally proposed testing strategy controls the Type I error at a pre-specified alpha level: testing both superiority for the primary endpoint and superiority for another endpoint in parallel after demonstrating non-inferiority for the primary endpoint and performing all three tests at the pre-specified alpha level may inflate the type I error in the trial. The objectives and testing strategy were modified to address these issues and to add a formal test for an important efficacy and safety endpoint (all-cause death).

a) the primary objective is to demonstrate non-inferiority on
The primary objective and the key secondary objective 2a are as originally specified in the protocol. The tests associated with the 4 objectives will be performed in a purely sequential manner which fully preserves the overall type I error in the trial (test 1; if 1 is met test 2a; if 2a is met test 2b, if 2b is met test 2c).

2) The second issue addressed in the present amendment is the resolution of a discrepancy in the interim analysis section regarding the stopping rule described in the protocol and the stopping rule described in the DMC charter (this stopping rule was developed with the input from the DMC members early on in the trial and prior to the DMC reviewing any trial data). The interim analysis section in the protocol was now modified to align with the rule described in the DMC charter.

3) The third reason is to increase the estimated study duration from 40 to 60 months. As noted in the Study Design and Duration section of the protocol this trial is event driven and the number of subjects required and the length of treatment are best estimates and based on event rates in similar trials. The previous protocol amendment (Amendment #7) increased the average duration of follow-up from 1.8 to 2.1 years due to the lower than initially estimated event rate, but the duration of the study was inadvertently left unchanged. This amendment is now documenting the extension of the duration of the trial. To support this extended duration, additional visits will be added to the time events schedule.

In addition the following will also be addressed:

4) Changing the name of the Protocol Manager

5) Providing clarification regarding the collection of blinded INR samples for subjects that discontinue or interrupt treatment.

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<td>01-Mar-2010</td>
<td>Increase the estimated study duration from 40 to 60 months and to add the additional to the time events schedule.</td>
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<td>Administrative Letter 04</td>
<td>03-Dec-2009</td>
<td>Changes the International emergency number for clinical trials, on the cover page. Updates the Serious Adverse Event (SAE) submission process. Confirms the use of the POC device for checking INRs prior to randomization and the central lab back-up process available for use in the event of a POC device failure. Clarify that compliance may be performed according to local regulations.</td>
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<td>05-Aug-2009</td>
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<td>The major rationale for this amendment is to increase the size of the patient sample size from 15,000 to 18,000. Additional changes include the requirement to report serious breaches to the sponsor; that patients may withdraw consent for study treatment but remain in follow-up; guidance on storage of IP; clarification of compliance by pill count of apixaban; refinement of the screening period for patients who enter the trial on warfarin or VKA, and are required to wait until their INR is &lt; 2.0 before beginning treatment.</td>
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<td>14-Jul-2008</td>
<td>Clarify participation in biomarker and outcome research assessment substudies is optional.</td>
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<td>Amendment 02</td>
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<td>This amendment was developed to address a number of specific needs: defines the goal and method of achieving enrollment of warfarin naive subjects; makes changes to inclusion and exclusion criteria to aid in enrollment while preserving safety; refines the dosing procedure for starting study drugs to take into account subjects who are on non-warfarin vitamin K antagonists; provides more detailed language regarding management of subjects at the times of elective and emergent surgery and invasive procedures, as well as in the event of bleeding; provides similar guidance at time of cardioversion; clarifies the number and types of restricted treatments, as well as the approach to discontinuation and follow-up to help minimize subjects who might be lost to therapy or to follow-up; the amendment provides an updated definition of the prospectively defined safety “events of special interest”; a publication plan is outlined; typographical errors and solecisms are corrected.</td>
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## SYNOPSIS

**Clinical Protocol CV185030**

**Title of Study:** Protocol CV185030: 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

**Estimated Number of Study Centers and Countries/Regions:** The study will be conducted in approximately 1000 sites in North and South America, Europe, Australia and Asia.

**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.

### 1. 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.

### 2. 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 ~9,000 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 ≤ 30 consecutive days of treatment with warfarin or another VKA in the past. Otherwise the subject will be classified as warfarin experienced.
3. 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 of up to 6 mg of warfarin (or warfarin placebo) 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 ≥ 80 years
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL

4. FOLLOW-UP PERIOD

Follow-up Visits: Follow-up of subjects who discontinued study drug prior to the attainment of 448 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 448 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.

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: An average of 18 subjects is expected per site for a total of approximately 18,000 subjects (9,000 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 2.1 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 2.1 years 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.

A Clinical Events Committee (CEC) will adjudicate all incidences of acute stroke, suspected systemic emboli, acute MI, cause of death, major bleeding events, and clinically relevant non-major bleeding events.

Adjudicated results will be the basis for the primary analyses.
An independent Data Monitoring Committee (DMC), separate from the CEC, will monitor the safety of all subjects during the study and give recommendations to the Study Steering Committee.

**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 for 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 determination:** The apixaban indication for prevention of stroke in AF patients may be supported by this single pivotal trial. Different regulatory agencies have different requirements for such a regulatory submission. Some agencies require a more stringent control of the type I error (one-sided 0.005 level rather than one-sided 0.025 level) in the presence of a single registrational trial. Others require a more stringent non-inferiority margin (1.38 rather than 1.44). Therefore,

A. in regulatory regions requiring a more stringent non-inferiority margin, the non-inferiority of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for RR is less than 1.38.

B. in regulatory regions requiring a more stringent control of the type I error, the non-inferiority of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.

The number of events required to achieve 90% power and meet the criteria described in (A) is lower than the number of events required to achieve 90% power and meet the criteria described in (B). This study is sized to meet the more stringent criterion. With 448 subjects with confirmed strokes or systemic emboli, the study will have at least 90% power to meet both regulatory definitions of non-inferiority described above. With an average 2.1 years follow-up and assuming a stroke rate of 1.20 per hundred patient-years, a total of approximately 18,000 randomized subjects allocated in a 1:1 ratio to the apixaban or warfarin group will be needed to achieve the desired power. These calculations assume an incidence of 1% loss to follow-up. Investigative site will be pooled to the geographic region level when including investigative sites as a stratification factor in a Cox proportional hazards model.

**Efficacy and Safety Analysis:** As noted above different agencies have different regulatory standards for demonstrating non-inferiority:

- in regulatory regions for which the criterion requires testing at one-sided 0.005 significance level and a non-inferiority margin of 1.44, non-inferiority will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.

- in regulatory regions for which the criterion requires testing at one-sided 0.025 significance level and a non-inferiority margin of 1.38, non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI for RR is less than 1.38.
For primary efficacy endpoint, tests using each non-inferiority margin will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin/VKA status (experienced, naïve).

If the primary objective is met then the hypotheses associated with key secondary objectives will be tested in a hierarchial fashion as outlined in Section 8.4.3.

For major bleeding, a point estimate and two-sided 95% CI for relative risk and a p-value for the test of equality of rates will be calculated. The test will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin/VKA status (experienced, naïve).
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1 INTRODUCTION AND STUDY RATIONALE

1.1 Research Hypothesis

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

1.2 Investigational Product Development Rationale

Apixaban is a novel, selective, orally active inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) as an anticoagulant and antithrombotic agent. Apixaban (formerly referred to as BMS-562247), is a reversible and highly potent inhibitor of human FXa, with an inhibitor constant ($K_i$) of $0.08 \pm 0.01$ nM, and a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

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), thereby 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. In the OASIS-5 trial of acute coronary syndromes, fondaparinux (at a dose of 2.5 mg subcutaneous per day) was shown to be equally effective in preventing thrombotic events as enoxaparin, but with half the bleeding risk. These findings highlight the potential of FXa inhibition to be an effective and safe approach towards anticoagulation. Given the established utility of FXa inhibition in prevention and treatment of venous and arterial thrombotic disease, an orally available agent would be desirable.
Thrombotic disorders are a major cause of mortality and morbidity. The Global Burden of Disease Study estimated that worldwide in 1990, over 6.3 million deaths were attributable to ischemic heart disease, and 4.4 million to stroke. More recent data from North America indicates that in 2001 over 920,000 cases of acute coronary syndrome (ACS), 250,000 cases of venous thromboembolism (VTE) and 930,000 cases of stroke were encountered. These conditions are a leading cause of premature morbidity and mortality; disordered thrombosis is an underlying contributing factor in their pathophysiology. Previous work has shown that effective antithrombotic therapy may treat or prevent ACS, VTE and stroke, but all of the presently available agents have liabilities. BMS has developed apixaban to overcome these limitations and 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. A Phase 2 dose-ranging study in the prevention of VTE in subjects undergoing total knee replacement surgery has been completed (CV185010). Other studies in Phase 2 development include dose-ranging trials in deep venous thrombosis (DVT) treatment (CV185017), secondary prevention in coronary artery disease subjects (CV185023) and a pilot study in VTE prevention in cancer subjects (CV185027).

1.3 Summary of Results of Investigational Program

Apixaban has undergone considerable in vitro and in vivo study in a wide variety of preclinical models; these findings are detailed in the investigator brochure.

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.

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. The study design and outcomes are discussed in Section 1.4.2 Rationale for Dose.
1.4 Study Rationale

1.4.1 Clinical Problem and Unmet Need

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. Data from the Framingham study confirm that AF is an independent risk factor for stroke, increasing the incidence five fold. 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.

Atrial flutter is a less common atrial arrhythmia than atrial fibrillation. In adults without congenital heart disease, atrial flutter frequently progresses to atrial fibrillation. Moreover, noninvasive testing (e.g. ECG, Holter monitoring) may yield the diagnosis of atrial flutter, only to be revised when intracardiac recordings demonstrate flutter activation of the right atrium and fibrillation of the left. The risk of thromboembolic stroke and systemic embolism is also increased in subjects with atrial flutter. A retrospective study of 749,988 subjects with either atrial fibrillation or atrial flutter calculated a stroke risk ratio (compared to those subjects without either arrhythmia) of 1.64 for the former and 1.41 for the latter. In comparison to atrial fibrillation, prospective, well controlled data are not as well developed for atrial flutter, but the available data support the conclusion that stroke risk is elevated in atrial flutter. For this reason the most recent ACC/AHA/ESC clinical guidelines state "it seems prudent to estimate the risk by the use of similar stratification criteria for both arrhythmias...". These guidelines further state: "Antithrombotic therapy is recommended for patients with atrial flutter as for those with atrial fibrillation".
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 importance of anticoagulation in this treatment approach was emphasized in the AFFIRM trial comparing rate control with rhythm control in subjects with AF. Stroke remained a major problem in the treatment groups, and it was particularly at issue in subjects whose anticoagulation had been stopped because of the belief that they were being successfully maintained in sinus rhythm. The authors concluded: “continuous anticoagulation is warranted in all subjects with AF and risk factor(s) for stroke, even when sinus rhythm appears to be restored and maintained.”

The coumarins or 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. Warfarin has also been shown to be superior to aspirin for this purpose in subjects with AF and additional risk factors for stroke (RRR 36%). Lastly, in the recent ACTIVE-W trial of subjects with AF and additional risk factors for stroke, warfarin was shown to be superior to a combination of aspirin and clopidogrel for prevention of stroke and other important vascular events.

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 of 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.\textsuperscript{14,15,16} 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) \textasciitilde60\% of the time.\textsuperscript{17,18} 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.\textsuperscript{19} In addition, recent studies have raised some concerns
regarding the effects of VKAs on bone metabolism.\textsuperscript{20,21,22} 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 conversely, 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. BMS has
developed apixaban as an antithrombotic for subjects with AF who are at risk for stroke
with the above properties in mind.

To establish the safety and efficacy of apixaban in the prevention of stroke and systemic
embolism in subjects with AF and stroke risk factor(s), BMS is undertaking the present
study (CV185030), a Phase 3 parallel arm study using warfarin as an active comparator.
Since warfarin has been shown to be highly effective in preventing stroke in this
population, a placebo controlled trial would not be ethical. The study will be randomized
and conducted in a double blinded fashion to minimize the risk of bias. A noninferiority
design will be employed (see Section 8 Statistical Considerations).
1.4.2 Rationale for Dose

The effectiveness of warfarin and other VKAs was first demonstrated in the treatment of DVT in the 1960s, prior to their study in AF clinical trials in the 1980s. Similar results were obtained with the low molecular weight heparins in VTE prevention and treatment, prior to their evaluation in ACS. In most cases, doses that are employed in venous thrombotic indications are the same or similar as those used in arterial indications or for atrial fibrillation: warfarin is dose adjusted to an INR of 2.0-3.0 for both DVT treatment and for stroke prevention in AF; enoxaparin is given at a dose of 30 mg BID or 40 mg QD for VTE prevention and at a higher dose of 1 mg/kg for DVT treatment and in ACS.

A 5 mg BID dose of apixaban is proposed for Phase 3 in AF. Selection of this dose was based primarily on the Phase 2 dose-ranging study in VTE prevention (CV185010), the ongoing Phase 2 study in DVT treatment (CV185017; 3 months treatment duration), and experiences with other anticoagulants studied in this patient population. In prior discussions with the Division of Cardio-Renal Drug Products at FDA and with the EMEA, it was agreed that Phase 3 AF dose selection for apixaban could be based on our Phase 2 DVT experience and would not require a Phase 2 experience in subjects with atrial fibrillation.

A Phase 2 apixaban study in AF has not been performed due to the expected low and variable event rates for stroke and major bleeding (~1 - 2% per year) that would not be adequately informative for identifying a Phase 3 dose. For example, in a Phase 2 study of ximelagatran in AF with approximately 60 subjects in each of 3 arms, there were no major bleeding events and only 2 TIA/CVA events, both of which occurred in the highest dose arm (60 mg BID). Dose selection for Phase 3 studies of ximelagatran in AF was instead based largely on the experience in VTE prevention, and the selected dose (36 mg BID) led to a stroke rate that was not deemed excessive relative to warfarin in 2 large trials (SPORTIF III and SPORTIF V).

Our Phase 2 VTE prevention study (CV185010) provided the basis for dose selection for the Phase 3 program in VTE prevention. Dose selection in VTE prevention was guided by the findings in Phase 2 as well as by an aim to optimize the benefit: risk relationship for apixaban in VTE prevention. For all apixaban arms in CV185010, the VTE/death
rates were at least 21% lower than the rate on enoxaparin 30 mg BID and at least 53% lower than the rate on warfarin. Physician surveys and consultant input consistently emphasized a preference for an apixaban dose that would not produce greater bleeding than observed for enoxaparin. Based on this consideration, the 2.5 mg BID and 5 mg QD doses were favored because both had rates of total bleeding that were lower than the rate for enoxaparin. To select between BID and QD doses, a regression analysis on the dose-response (Figure 1.4.2) and a population PK analysis of the exposure-response were performed. Each of these analyses suggested that the 2.5 mg BID dose had greater efficacy than the 5 mg QD dose by ~4% on the primary endpoint (i.e., ~25% additional RRR versus enoxaparin).

Figure 1.4.2: Observed and Fitted VTE/Death Rates in study CV185010

![Observed and Fitted VTE/Death Rates](image)

The 2.5 mg BID dose was therefore selected for Phase 3 in DVT prevention. This dose demonstrated a 36% RRR in VTE/all cause death vs enoxaparin and a 63% RRR vs. warfarin, was not associated with major bleeding, and had an incidence of total bleeding
that was lower than for enoxaparin. Overall safety was comparable for apixaban 2.5 mg BID and enoxaparin.

A 5 mg BID dose was selected for AF. Compared to VTE prevention, for which bleeding safety was the primary consideration for dose selection, in AF increased emphasis on efficacy for dose selection is required due to significant consequences of stroke. This favored the selection of 5 mg BID rather than the 2.5 mg BID dose, as this dose appeared to have increased efficacy without substantial incremental increase in major bleeding. Apixaban doses greater than 5 mg BID had even greater efficacy, but the bleeding risk appeared to outweigh the incremental efficacy, so these higher doses were not selected for the AF study.

As for DVT prevention, BID dosing rather than QD dosing was selected for AF due to our belief that maintained trough levels and low peak-trough ratios are important for efficacy to reduce the stroke rate in AF and for safety to reduce the bleeding rate. Data from CV185010 suggest the importance of maintained trough levels for optimal antithrombotic efficacy. In a recently reported Phase 2 study of dabigatran in AF (PETRO, with open-label extension, European Stroke Conference; May 2006), 2 of the dabigatran dose arms were 150 mg BID and 300 mg QD. Despite the same daily dose, the BID arm had a 0.7% stroke rate and the QD arm had a 9.5% stroke rate. Although full details of the design and results are not yet available, these findings also suggest that maintained trough levels are important for preventing stroke.

Additional data regarding the 5 mg BID dose are available from the ongoing DVT treatment study (CV185017). CV185017 includes 3 blinded apixaban arms (5 mg BID, 10 mg BID, 20 mg QD) and an open-label warfarin arm. A planned interim analysis performed in August, 2006, when half of the expected 520 subjects had been randomized, led the DSMB to advise that the study proceed without modification. Ongoing interim efficacy and safety data from this study further support the initiation of a long-term trial of 5 mg BID in AF. Three-month treatment with apixaban at up to 20 mg daily has not been associated with excess bleeding or hepatotoxicity.

In CV185017, as of September-2006, in 240 patients receiving apixaban, there have been 4 (1.7%) VTE events compared with 3 (4.0%) VTE events in 76 warfarin-treated subjects. Prior DVT treatment studies have demonstrated that under treated acute DVT
has a high recurrence rate (~ 25 - 30%) within 90 days of initial therapy, and that warfarin therapy substantially reduces this rate.\textsuperscript{28,29} The low rate of VTE observed in apixaban-treated patients with acute DVT demonstrates that effective antithrombotic activity is achieved with the doses used in CV185017, including the 5 mg BID dose to be used in the AF study.

In CV185017, as of September-2006, there have been no major bleeding events on apixaban or warfarin. There have been 11 (4.6%) clinically relevant non-major bleeding events on apixaban and 4 (5.4%) on warfarin. There have been 4 (1.7%) occurrences of ALT elevation $> 3x$ upper limit of normal (ULN) on apixaban, 2 of which appear unrelated to apixaban, and 2 (2.6%) ALT elevations on warfarin.

In summary, 5 mg BID is our proposed dose in Phase 3 AF, as it appears to provide the best balance of efficacy and safety. Furthermore, an optimal dose of apixaban is likely necessary to match the efficacy of warfarin in a clinical trial with carefully controlled INR levels.

As described in Section 5.3.1, certain subjects who may be deemed to be at higher risk of bleeding, will be administered a lower, 2.5 mg BID dose of apixaban (or matched placebo).

1.5 Overall Risk/Benefit Assessment

Apixaban has undergone extensive clinical and preclinical testing. Full details of these studies appear in the investigator brochure. 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.

Apixaban had no adverse fetal effects when given orally to rats (100 to 3000 mg/kg/day) or intravenously to rabbits (1.25 to 5 mg/kg/day). Fetal exposures were confirmed. Maternal toxicity (red perivaginal substance and mucoid feces) was noted in rats but not
rabbits. Animal-to-human exposure multiples at the fetal NOAEL were 35x and 3.1x for rats and rabbits, respectively relative to a clinical dose of 5 mg BID. Although post-implanation loss was slightly increased in pregnant mice given the highest dose of apixaban tested in an oral range-finding study (1500 mg/kg/day; 16x human exposure at 5 mg BID), postimplantation loss was not increased in the follow-up definitive study (preliminary data) indicating the previously noted increase was not due to apixaban. Administration of warfarin to pregnant women has been reported to cause birth malformations in children. A higher risk of fetal mortality (fatal hemorrhage, spontaneous abortion and stillbirth), low birth weight, and growth retardation have also been associated with the use of warfarin in pregnant women (see product label).

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.

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.

The overall frequencies of AEs, significant AEs, deaths, and discontinuation for adverse events were similar across treatment groups in this study (Table 1.5). For AEs other than those related to bleeding, there was no dose-response in the apixaban-treated groups and no notable differences from enoxaparin- or warfarin-treated groups. The frequency of liver enzyme elevations was low for all apixaban-treated groups and less than the rate for the enoxaparin-treated group.
Liver function testing in the CV185010 trial revealed an incidence of ALT > 3x ULN in 0.9% of apixaban-treated subjects compared with 3.1% of enoxaparin-treated subjects and 0.8% of warfarin-treated subjects. In the ongoing CV185017 Phase 2 DVT treatment study, the incidence of ALT ≥ 3x ULN was 1.7% in the apixaban-treated groups, and 2.6% in the VKA-treated group (as of September 2006, N = 316).

Apixaban provides a number of potential benefits. In addition to its potent, predictable and lasting anticoagulant activity, it does not require therapeutic monitoring to be administered safely. It is available for oral administration without a food effect on absorption and is simple to dose. It has a well behaved pharmacokinetic profile and low toxicity. It does not have the same potential for drug and botanical interactions as warfarin, and has a wider therapeutic index. These features may make it superior to currently available alternatives, thus addressing an unmet clinical need.

In summary, apixaban has a low incidence of adverse effects and a low incidence of bleeding. The major risk of subjects participating in the proposed study would be a failure of efficacy, resulting in an increased risk of stroke. To some extent, efficacy is always at issue when conducting a clinical trial with a new drug in a setting where outcomes are serious events associated with mortality or substantial morbidity. To minimize this risk, BMS has conducted careful preclinical and clinical studies to confirm the antithrombotic efficacy of apixaban in a number of relevant models. The results of the previous VTE prevention trial (CV185010) demonstrate that apixaban, at a dose of 5 mg BID is better than either enoxaparin or warfarin on its point estimate of efficacy; this was achieved without excessive bleeding. The interim data from the ongoing DVT treatment
study (CV185017) confirm these data. Lastly, a comparison of these findings with findings of the ximelagatran development program suggest that apixaban’s antithrombotic efficacy should be as good or better than ximelagatran, whose stroke rate in AF trials was not excessive. Finally, to guard against undue risk in the program events will be adjudicated by independent clinical events committee (CEC), and the conduct of the trial supervised by an independent data monitoring committee (DMC).

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

2.2.1 Key Secondary Objectives

The key secondary objectives are 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

2.2.2 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

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.

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 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).
Systems with procedures that assure the quality of every aspect of the study will be implemented.

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The Investigator or sponsor should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 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.

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.

Subjects may withdraw consent from participation in the study at any time, however BMS will request periodically (approximately every 3 months) that endpoint and survival
data be collected on all subjects. At this time, each subject will be contacted to determine if an endpoint has occurred and/or regarding survival status. Investigative sites may contact subjects by telephone and/or certified letter, if necessary, to obtain endpoint and survival information. Every attempt should be made for the closeout study visit to be performed in person; a telephone contact is permissible only if a face-to-face visit is not possible (see Section 5.7, End of Study). The site must document all attempts to contact the subject in the medical record. If it is determined that a subject has died, the investigative site will use appropriate methods approved by the Institutional Review Board/Ethics Committee to obtain consent for release of the date of death to site personnel.

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. If a subject’s information cannot be obtained by other methods, a locator company will be employed where permitted by local authorities to obtain this information. This is particularly important if the subject withdraws his/her consent after experiencing an AE/SAE or an efficacy endpoint since for safety purposes, it is necessary to obtain information regarding worsening or resolution of the event.

If a subject is lost to follow-up and cannot be contacted or data obtained by any IRB/EC approved means, then a waiver should be requested from the IRB/EC (where possible and allowed by local law) and the date of last known contact as determined by the primary investigator or referring physician should be reported.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

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.
Minors who are judged to be of an age of reason must also give their written assent.

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.

Appendix 1 contains BMS procedures on obtaining informed consent from subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative prior to participating in a clinical study. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable (see subject selection criteria in Sections 4.2.1 and 4.2.2).

4 INVESTIGATIONAL 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, (see Section 8.1), 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 448 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 ~9,000 subjects (for a total of ~18,000 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. The two sets of tablets each subject receives will be distinguishable by color and size, but active apixaban tablets will match placebo apixaban tablets and active warfarin tablets will match placebo warfarin tablets to avoid unblinding of investigators and staff.

INR testing frequency will occur at least every month during the treatment period, more frequently during titration and if clinically indicated (see Section 5.3 Selection and Timing of Dose for Each Subject). 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.

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 448 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 448 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 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 448 primary efficacy events; and (3) a follow-up period lasting until the latter of 30 days after treatment discontinuation or the attainment of 448 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), led by co-chairs Dr. Lars Wallentin (Uppsala University Hospital) and Dr. Chris Granger (Duke University Medical Center), 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 membership, roles and responsibilities of the Executive Committee are further described in a Executive Committee Charter. 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. The Executive Committee will oversee a Steering Committee which will include the Executive Committee and National and/or Regional Coordinators. The Steering Committee members will be responsible for operational aspects of the study in their countries/regions and will report potential issues
and recommendations to the Co-Chairs of the Executive Committee. There will be regular joint meetings of the Executive and Steering Committees to monitor the progress of the study and address any emerging issues.

4.1.2 Operations Committee

The Operations Committee (OC) will consist of a small group of Executive Committee members chosen for their specific expertise and experience as well as representatives of the sponsor and CRO. This group will be responsible for ensuring that study execution and management are of the highest quality. The Operations Committee will convene regularly by teleconference and/or face-to-face meeting (at least every 2 months) to discuss and report on the ongoing conduct of the study.

4.1.3 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. The chairman of the CEC will be Dr. John Alexander (Duke University Medical Center).

4.1.4 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 have a chairperson (Dr. Marc Pfeffer, Brigham and Women’s Hospital, Boston) 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 (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. An initial recommendation for stopping the trial will be made by the DMC. The final recommendation to terminate the study will be made by the Operations Committee of the Executive Committee to the sponsor after considering the recommendation of the DMC.

Safety events, and more specifically severe bleeding, will be monitored. No formal stopping boundaries are proposed in the protocol but clear, consistent, and persistent evidence of net harm that overwhelms any benefit should be apparent; formal boundaries to stop early for safety reasons may be proposed in the DMC charter. A recommendation to stop the trial will be based on the pattern of treatment effect across all endpoints, as well as the consideration of benefit/risk.

4.2 Study Population

4.2.1 Inclusion criteria

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

1) Age $\geq$ 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

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).

3) One or more of the following risk factor(s) for stroke:
   a) Age 75 years or older
   b) Prior stroke, TIA or systemic embolus
   c) Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with an LV ejection fraction (LVEF) $\leq$ 40% by echocardiography, radionuclide study or contrast angiography
d) Diabetes mellitus  

e) Hypertension requiring pharmacological treatment

4) 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.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level > 35 mIU/mL). Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to the start of investigational product.

4) All subjects must provide **signed written informed consent**.

### 4.2.2 Exclusion criteria

5) Atrial fibrillation or flutter due to reversible causes (e.g., thyrotoxicosis, pericarditis)

6) Clinically significant (moderate or severe) mitral stenosis

7) Increased bleeding risk that is believed to be a contraindication to oral anticoagulation (e.g., previous intracranial hemorrhage)

8) Conditions other than atrial fibrillation that require chronic anticoagulation (e.g., prosthetic mechanical heart valve)

9) Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, or diastolic BP > 100 mm Hg)

10) Active infective endocarditis
11) Planned major surgery
12) Planned atrial fibrillation or flutter ablation procedure
13) Use of an unapproved, investigational drug or device within the past 30 days
14) Required treatment with aspirin > 165 mg/day
15) Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)
16) Severe comorbid condition with life expectancy of ≤ 1 year
17) Active alcohol or drug abuse, or psychosocial reasons that make study participation impractical
18) Recent ischemic stroke (within 7 days)
19) Severe renal insufficiency (serum creatinine > 2.5 mg/dL or a calculated creatinine clearance < 25 mL/min, See Section 6.3.2.2)
20) ALT or AST > 2X ULN or a Total Bilirubin ≥ 1.5X ULN (unless an alternative causative factor [e.g., Gilbert’s syndrome] is identified)
21) Platelet count ≤ 100,000/ mm³
22) Hemoglobin < 9 g/dL
23) Inability to comply with INR monitoring
24) Prior randomization into an apixaban clinical study
25) Prisoners or subjects who are involuntarily incarcerated
26) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
27) Women of child bearing potential (WOCBP) unwilling or unable to use an acceptable method to avoid pregnancy:
   a) WOCBP using a prohibited contraceptive method
   b) WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]. Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of child bearing potential
c) Women who are pregnant or breastfeeding

d) Women with a positive pregnancy test on enrollment or prior to administration of investigational product.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue study treatment (investigational or noninvestigational 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
- Clinical jaundice is present for a subject at any time
- If ALT ≥ 5 x ULN on any two consecutive occasions
- Total bilirubin ≥ 2.0 x ULN on any two consecutive occasions in the absence of an alternative causative factor [e.g., Gilbert’s syndrome] is identified
- Pregnancy (see Section 7.6.2)
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (e.g., infectious disease)

There should be continued attempts throughout the duration of the trial, if clinically appropriate, to resume study medication for any subject who has had study drug discontinued. If, in the judgment of the investigator, the subject cannot continue to receive study treatment, or if the subject withdraws consent, then continued follow-up will be pursued with the subject, the subject’s family or designated representative to ascertain the subject’s vital status.
All subjects who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures including follow-up, or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject discontinues study treatment the reason for discontinuation must be entered on the appropriate case report form (CRF) page.

5 TREATMENTS

5.1 Study Treatment

5.1.1 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

5.1.2 Noninvestigational Product

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products.
5.1.3 Identification

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

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>POTENCY</th>
<th>APPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (BMS-562247) film coated tablets</td>
<td>5 mg</td>
<td>Reddish brown, plain, oval shaped, shallow biconvex film coated tablet</td>
</tr>
<tr>
<td>Apixaban (BMS-562247) film coated tablets</td>
<td>2.5 mg</td>
<td>Reddish brown, plain, oval shaped, shallow biconvex film coated tablet</td>
</tr>
<tr>
<td>Placebo for apixaban (BMS-562247) film coated tablets</td>
<td>-</td>
<td>Reddish brown, plain, oval shaped, shallow biconvex film coated tablet</td>
</tr>
<tr>
<td>Warfarin Sodium (BMS-565793) tablets</td>
<td>2 mg</td>
<td>Lavender, round, biconvex tablet with one face bisected and the other face plain</td>
</tr>
<tr>
<td>Placebo for Warfarin Sodium (BMS-565793) tablets</td>
<td>-</td>
<td>Lavender, round, biconvex tablet with one face bisected and the other face plain</td>
</tr>
</tbody>
</table>

5.1.4 Packaging and Labeling

Randomized Double-Blind Treatment:

At the time of randomization, each subject will receive two bottles. One bottle will contain 200 film-coated tablets of apixaban (BMS-562247) or matching placebo. The second bottle will contain 100 tablets of warfarin sodium 2 mg tablets or matching placebo.

Each apixaban/placebo bottle will be labeled with a 3-panel, double-blind yellow label printed in black ink (except for batch number OA58966 only where each apixaban/placebo bottle will be labeled with a 3-panel, double-blind white label printed in black ink). On this label the protocol number, blinded batch number, container number, blinded drug name, tablet quantity, storage conditions, directions for use and route of administration will be indicated. Subjects will be re-supplied with a new bottle of apixaban/placebo tablets every 3 months.

Each warfarin/placebo bottle will be labeled with a 3-panel, double-blind white label printed in black ink. On this label the protocol number, blinded batch number, container
number, blinded drug name, tablet quantity, storage conditions, directions for use and route of administration will be indicated. Subjects will be re-supplied with a new bottle of warfarin/placebo tablets as needed based on their dose titration and will be managed through the Interactive Voice Response System (IVRS).

The third panel contains the unblinding information. In the event of a medical emergency, the panel may be opened by the treating physician. The Investigator must record the nature of the emergency that required breaking the code and must notify the Medical Monitor (see Section 7.3.1).

5.1.5 Handling and Dispensing

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The Investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light and humidity) as determined by the sponsor. Apixaban/placebo tablets should be stored at 15 - 25°C and warfarin/placebo tablets should be stored at 15 - 30°C, protected from light and protected from moisture. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact the sponsor immediately.

Refer to Section 9.2.2 for information on investigational product record retention and 9.3 for return and destruction instructions.

5.1.6 Retained Samples for Bioavailability/Bioequivalence Studies

Not applicable.

5.2 Method of Assigning Subjects to a Treatment

At the time of enrollment, each subject will be assigned a unique sequential subject number by the IVRS. 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). Assignment will be in a 1:1 ratio by the IVRS. Randomization schedules will be generated and kept by BMS. At the time of randomization, the IVRS will assign each subject two container numbers (warfarin/warfarin-placebo and apixaban/apixaban-placebo). Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the bottles containing study medication. Container numbers will be recorded on the CRF.

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 ≤ 30 consecutive days of treatment with warfarin or another VKA in the past. Otherwise the subject will be classified as warfarin experienced.

Inclusion of a sufficient proportion of warfarin naïve subjects is essential if the study is to achieve its stated goals (see Section 5.2). To ensure this, sites are required to enroll and randomize a minimum percentage of subjects as warfarin naïve. At each site, at least 40% of subjects randomized should be warfarin naïve. The IVR system used to enroll and randomize subjects will require these targets at the time of randomization. In addition, the number of warfarin experienced subjects may be capped at 9,000.

5.3 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.

5.3.1 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:

- Age ≥ 80 years
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL

5.4 Blinding/Unblinding

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.
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.

**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.

Every subject will be provided with an alert card. The alert card:

- Will indicate that the subject is participating in a double-blind clinical trial
- Provides the sponsor’s name (Bristol-Myers Squibb) and trial number (CV185030)
- Will note that the subject may be receiving either warfarin or an investigational anticoagulant drug (a factor Xa inhibitor)
- Includes contact numbers for the subject’s investigator to provide information to emergency medical personnel

The need to break the blind must first be discussed with the responsible Medical Monitor. A trial help line may also be used be for this purpose.
5.4.1 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)

5.4.1.1 Elective Procedures

In general, local standards of care for discontinuation of anticoagulation prior to elective procedures/surgery should be employed; these may be informed by current guidelines.\(^\text{10}\) These are summarized below based upon the risk of thromboembolism:

Low risk of thromboembolism

- Stop warfarin/warfarin-placebo and apixaban/apixaban-placebo 4 days before the planned procedure.
- Monitor the INR using the encrypted POC device as necessary.\(^*\)
- 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.
- If the procedure is associated with an increased risk of thrombosis, brief postoperative protection with UFH or LMWH at a prophylactic dose may be considered.
- Restart warfarin/warfarin-placebo (usually the night of the day of surgery) and apixaban/apixaban-placebo postoperatively (usually the day after surgery) when it is deemed safe to do so. If UFH/LMWH is used in the postoperative period, begin apixaban/apixaban-placebo when the INR is therapeutic.

\(^*\) Note that the encrypted POC device will provide the true INR for subjects receiving warfarin, and a shammed INR for those receiving apixaban. The shammed value will decline, as it is based on the most
recent warfarin placebo “doses”, which will be nil (since they are being held prior to the planned procedure). Thus the POC INR will reflect the true INR for subjects randomized to warfarin, while preserving the blind in all subjects.

Intermediate risk of thromboembolism

- Stop warfarin/warfarin-placebo 4 days before the planned procedure.
- Monitor the INR using the encrypted POC device as necessary.
- Two days before the planned procedure, stop the apixaban/apixaban-placebo and begin UFH or LMWH. The doses employed should conform to the local standard of care.
- 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/LMWH during the postop period (full dose preferred over prophylactic dose) 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 and when it is deemed safe to do so. Stop UFH/LMWH.

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.
5.4.1.2 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 (see Section 5.4 Blinding/Unblinding). 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).

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. Given its half-life (12 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Depending on the subject’s risk of bleeding with the procedure, subjects receiving apixaban who require an invasive or surgical procedure within 24 hours of their last dose may be treated with prophylactic peri-procedural FFP (2 units IV every 6 hours) at the discretion of the local physician and investigator.

If treatment with an alternative open label anticoagulant/antithrombotic is indicated for the procedure, it should be used at the lowest therapeutic dose (if at all) in the 12 hours following last dose of apixaban. Interactions between apixaban and other antithrombotics (with the exception of aspirin and clopidogrel) have not been evaluated.
A suggested strategy (based on present guidelines) for bridging AF subjects at low risk for thromboembolism through surgery or an invasive procedure is depicted in Figure 5.4.1.3A. Both study drugs are discontinued four days prior to the planned procedure. INR monitoring is performed using the encrypted POC device. When the INR falls to a value low enough to permit the procedure, an open INR is obtained at a local laboratory to confirm the result prior to the procedure. After the procedure, warfarin (or its placebo) is restarted, generally on the evening of the day of surgery. POC monitoring of the INR is initiated. If bridging with UFH/LMWH is desired (for example, after PCI), it is begun at this time, and apixaban (or its placebo) is not begun until after the POC INR is ≥ 2.0, when the UFH/LMWH is discontinued. If no UFH/LMWH is used, then apixaban (or its placebo) is begun at the time that warfarin (or its placebo) is restarted.
Figure 5.4.1.3B: Bridging Strategy for Intermediate and High Risk AF Subjects

A diagram of the suggested approach to elective invasive procedures/surgery in subjects deemed at intermediate or high risk of thromboembolism is shown in Figure 5.4.1.3B. Warfarin/warfarin-placebo is discontinued 4 days prior to the planned procedure and the INR monitored with the encrypted POC device. When the INR falls below 2.0 (about 2 days prior to the procedure) full dose UFH or LMWH is begun, and apixaban/apixaban-placebo discontinued. An open INR is obtained prior to the procedure at a local laboratory. After the procedure, warfarin (or its placebo) is restarted, generally on the evening of the day of surgery. POC monitoring of the INR is initiated. Bridging with UFH/LWH is begun, generally at full dose. When the POC INR ≥ 2.0, UFH/LWH is discontinued, and apixaban (or its placebo) is restarted.
5.5 Concomitant Treatments

5.5.1 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

The decision to employ dual anti-platelet therapy (with aspirin and a thienopyridine such as clopidogrel or ticlopidine) in subjects on study drug may arise at the time of acute coronary syndrome or percutaneous coronary intervention. There are few data from randomized clinical trials of dual anti-platelet therapy in the setting of oral
anticoagulation with either vitamin K antagonists or apixaban. Nevertheless, there is a heightened concern regarding bleeding in this setting. The determination to employ concomitant dual anti-platelet therapy in subjects anticoagulated with study drug should respect this concern and be made carefully by the investigator or treating physicians after careful consideration of the risks and potential benefits.

In addition, if a subject is currently receiving an agent that is a potent inducer of CYP3A4 (e.g., rifampin), the investigator should carefully evaluate that subject’s risk of thromboembolism, as the plasma concentration of apixaban may be lower than that in subjects not receiving a potent inducer of CYP3A4.

5.5.2 Other Restrictions and Precautions

The following precautions and restrictions must be followed to preserve study integrity and subject safety:

- Subjects should comply with the prescribed dosing and visit schedule
- Subjects should be instructed that prior to taking any new prescriptions and/or over-the-counter medications, they should discuss this thoroughly with the Investigator to ensure the new medication is not prohibited by the study protocol.

Since apixaban is a direct inhibitor of FXa, it acts as an anticoagulant. The safety of apixaban in combination with other anticoagulants such as unfractionated heparin, low molecular weight heparin, or fondaparinux, has not been evaluated. Thus, it is preferable to stop blinded study drug to allow for its clearance from the body prior to initiating treatment with another anticoagulant or performing invasive procedures. In normal human volunteers, apixaban has an effective half-life of 10 - 15 hours. The anticoagulant effects of apixaban persisting more than 24 hours after the last dose would be expected to be minimal. Since apixaban given alone in single and multiple dose studies has been shown to be safe even at daily doses five times greater than those used in the current study, it is likely that effective hemostasis can be achieved even at shorter times after the last dose if the need for urgent interventions is deemed high. Investigators should contact the Medical Monitor/Trial Helpline to discuss initiation of other anticoagulants for a study subject.
5.5.3 Management of Cardioversion

Cardioversion, both spontaneous and as the result of medical intervention, is an important clinical issue for subjects with atrial fibrillation. Many of the subjects randomized to the study will spontaneously convert to and from atrial fibrillation during the trial, often on more than one occasion. It is important to assess the effectiveness of apixaban as compared to warfarin in preventing stroke in these subjects, and in subjects in whom cardioversion is induced either electrically or by the use of an antiarrhythmic drug. In general, subjects entered in the trial should receive blinded oral anticoagulation with therapeutic INRs for at least 3 weeks prior to undertaking elective cardioversion (either electrical or chemical) as is recommended in current guidelines.

In certain subjects at higher risk for left atrial or left atrial appendage thrombus, transesophageal echocardiography may be a useful adjuvant in guiding clinical decision making.

The DMC will review adverse event data from subjects undergoing cardioversion during the course of the study.

5.6 Treatment Compliance

Apixaban study drug pill count will be performed at each scheduled visit for all subjects or as per local regulations. The need for compliance with study drug administration will be reinforced at each study visit.

5.7 End of Study

The Sponsor will estimate the End of Treatment Period date (EOTP, the date when it is estimated that 448 primary efficacy events will have occurred), and will communicate, in advance, this date to sites.

5.7.1 Final Treatment Visit

All sites should perform the final treatment (FTV) visit for all subjects who have not permanently discontinued study drug as close as possible to the EOTP date and no more than 5 weeks after the EOTP date.
In the unusual event that a subject cannot return to the site for the final treatment visit within 5 weeks after the EOTP date, a phone call should be made (within 5 weeks of the EOTP date) to perform the assessment of serious adverse events (SAEs), study outcome events (SOEs), adverse events, concomitant medications and fractures. Instructions should be provided regarding administration of the last dose of study medication and the initiation of anticoagulant therapy. Arrangements should be made for follow-up care and the return of study medication.

5.7.2 Switching from Study Drug to Open Label Standard of Care

The following method is recommended to switch subjects from double-blind study drug to open-label standard of care.

The subject takes the morning dose of blinded apixaban (apixaban/placebo), either at home, on the morning of the FTV. The blinded warfarin (warfarin/placebo) study medication containers are collected at the FTV, and the bottle of apixaban/apixaban-placebo study drug is redispensed to the subject with four tablets of the apixaban/apixaban-placebo study drug inside. Open label warfarin (or VKA) is prescribed by the investigator— if the subject has had a stable INR during the months prior to EOTP date, then it would be reasonable to consider the recent dosing schedule of blinded warfarin as a starting point for the open label warfarin dose; but the final decision regarding warfarin (or VKA) dose rests with the investigator. Subjects on very low doses (2 mg/day or less) or higher doses (> 6mg/day) of blinded warfarin should have their dose considered carefully, since if they are receiving warfarin placebo, continuation of such dosing may affect the degree of anticoagulation initially achieved. Switching is accomplished using an “apixaban bridge” by the following schedule, (Switch Day 1 is the day of the FTV):

- Switch Day 1 (PM): Subject takes open label warfarin (or VKA) dose AND one blinded apixaban tablet.

- Switch Day 2 (AM): Subject takes one blinded apixaban tablet.

- Switch Day 2 (PM): Subject takes open label warfarin (or VKA) dose AND one blinded apixaban tablet.
• Switch Day 3 (AM): Subject takes one blinded apixaban tablet.

• Switch Day 3 (PM): Subject takes open label warfarin (or VKA) dose.

It is recommended that the subject return on Switch Day 3 or Switch Day 4 for an open INR measurement, and that future warfarin (or VKA) dosing decisions be based upon this and subsequent INR measurements. INR monitoring should be performed as if the subject is being newly titrated onto warfarin (or VKA). The investigator may relinquish subsequent warfarin (or VKA) treatment to the subject’s personal physician or to an anticoagulation clinic when it is prudent to do so, based upon clinical judgment and the local standard of care. The blinded apixaban container is collected at this visit and final drug reconciliation for this bottle is performed.

Investigators, at their discretion, may choose to switch subjects to open label warfarin (or a VKA) without overlapping with blinded apixaban, or they may choose to use low molecular weight heparin or unfractionated heparin bridging instead in appropriate cases, or they may chose to switch the subject to another antithrombotic drug (e.g. aspirin or a novel oral anticoagulant) that is approved for this use in their country based on local standards of care. If switching is accomplished without using the apixaban bridge, then all blinded study medication should be collected and reconciled at the FTV visit.
6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Flow Chart/Time and Events Schedule

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Day 1</th>
<th>Day 4, Week 1, Day 10, Week 2, Week 3</th>
<th>Months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, 47, 49, 50, 52, 53, 55, 56, 58, 59 (INR)</th>
<th>Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57</th>
<th>Months 12, 24, 36, 48</th>
<th>Final Treatment Visit a</th>
<th>Follow-up</th>
<th>Protocol Section</th>
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<tbody>
<tr>
<td>Eligibility Assessments</td>
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Revised Protocol No.: 04
Date: 04-Aug-2010
Table 6.1: Flow-Chart/Time and Events Schedule

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<th>Day 4, Week 1, Day 10, Week 2, Week 3</th>
<th>Months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, 47, 49, 50, 52, 53, 55, 56, 58, 59</th>
<th>Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57</th>
<th>Months 12, 24, 36, 48</th>
<th>Final Treatment Visit a</th>
<th>Follow-up b</th>
<th>Protocol Section</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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Date: 04-Aug-2010
### Table 6.1: Flow-Chart/Time and Events Schedule

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Day 1</th>
<th>Day 4, Week 1, Day 10, Week 2, Week 3</th>
<th>Months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43, 44, 46, 47, 49, 50, 52, 53, 55, 56, 58, 59</th>
<th>Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, 57</th>
<th>Months 12, 24, 36, 48</th>
<th>Final Treatment Visit</th>
<th>Follow-up</th>
<th>Protocol Section</th>
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<tbody>
<tr>
<td>INR (POC)(^1)</td>
<td></td>
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<td>Urinalysis(^h)</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>m</td>
<td>6.7</td>
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<tr>
<td><strong>Clinical Drug Supplies</strong></td>
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<td>Dispense Study Treatment</td>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>n</td>
<td>5.3</td>
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<tr>
<td>Assessment of Study Medication Use</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>6.1.5</td>
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<tr>
<td>Assessment of Concomitant Med Use</td>
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<td></td>
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<td></td>
<td></td>
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<td>5.5.1, 6.3.8</td>
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<tr>
<td>Collect Study Medication</td>
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<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>n</td>
<td>6.1.5</td>
</tr>
</tbody>
</table>

\(^1\) INR (POC): Performed at the beginning of the study and at the discretion of the investigator.

\(^h\) Urinalysis: Assessed at the discretion of the investigator.

\(^m\) Genomic Blood Draw: Assessed at the discretion of the investigator.

\(^n\) Collect Study Medication: Assessed at the discretion of the investigator.
Please refer to FTV procedures (See Section 5.7.2). If bridging with blinded apixaban is performed, this visit may be completed over multiple days.

If the subject discontinued study treatment prior to the EOTP, it is preferable that the final follow-up visit be performed in person.

Weight, and hip and waist circumference only.

ECG can be performed within two months prior to FTV visit.

At Months 6, 18, 30, 42 and 54 only.

Month 1 only

Assess for SAEs only for the first 30 days after the last dose of double-blind study drug.

All protocol-specific laboratory tests will be analyzed by a central laboratory. The laboratory tests scheduled at the FTV visit can be performed within two months prior to FTV visit.

Full chem 21 panel

Chem 7 panel

Lab draw for LFT and CK assessment only at the Months 1, 2, 6, 18, 30, 42 and 54 visits.

All INR measurements, except for the screening visit, will be collected using the Point of Care (POC) device provided. INR measurements will be performed on Day 4, twice a week for two weeks, once a week for two weeks, (i.e. on Day 4, Week 1, Day 10, Week 2, Week 3, Week 4) and monthly thereafter during the treatment period. If the INR was >2.0 at the screening visit, the POC device may be used at Day 1 to determine if the INR is < 2.0 prior to randomization. See section 6.1.5.2 for details.

The genomic lab draw should be performed at the Month 2 visit, however, it may be drawn at any scheduled lab collection visit after randomization.

If bridging is performed to switch subjects from double-blind study drug to open label standard of care, blinded apixaban will be redispensed at the final treatment visit and collected for final reconciliation after the final dose of blinded apixaban is administered. Blinded warfarin should be collected at the FTV.
6.1.1 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 (see Section 5.3, Selection and Timing of Dose for Each Subject).

Treatment Period

- Lasting until the earlier of a subject’s treatment discontinuation or the attainment of 448 primary efficacy events

Follow-up Period

- Lasting until the latter of 30 days after treatment discontinuation or the attainment of 448 primary efficacy events

6.1.2 Visit Windows

The procedures scheduled at each visit may be performed on days other than the nominal days specified in the table in Section 6.1. The allowed deviations from the nominal visit days are tabulated below:

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Visit Days/Allowed Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 1</td>
</tr>
<tr>
<td>Day 4</td>
<td>Day 4 or Day 5</td>
</tr>
<tr>
<td>Week 1</td>
<td>Day 7 or 8</td>
</tr>
<tr>
<td>Day 10</td>
<td>Day 10 or 11</td>
</tr>
<tr>
<td>Week 2</td>
<td>Day 14 or 15</td>
</tr>
<tr>
<td>Week 3</td>
<td>Day 21 or 22</td>
</tr>
<tr>
<td>Month 1</td>
<td>± 4 days</td>
</tr>
</tbody>
</table>
### Table 6.1.2: Visit Window

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Visit Days/Allowed Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months 2 - 59</td>
<td>± 7 days</td>
</tr>
<tr>
<td>Final Treatment Visit</td>
<td>0-35 days after the EOTP date (448 primary efficacy events attained)</td>
</tr>
<tr>
<td>Quarterly Follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td>± 14 days</td>
</tr>
<tr>
<td>30 Day Follow-up&lt;sup&gt;b&lt;/sup&gt;</td>
<td>± 7 days</td>
</tr>
</tbody>
</table>

<sup>a</sup> Applicable only to subjects who discontinued double-blind study drug prior to FTV. Subjects may choose not to participate in quarterly follow-up, but may still be contacted on or after the EOTP regarding endpoint information/survival data.

<sup>b</sup> The 30 days follow-up phone call should be performed 30 ± 7 days after the FTV. If the subject discontinued double-blind study drug prior to the EOTP date, it is preferable for this visit to be performed in person. For these subjects, this visit can be performed anytime within 30 days after the EOTP date but not sooner than 3 weeks after the last dose of double-blind study drug.

### 6.1.3 Screening Period, Period B - Enrollment Visit

The Investigator or designee 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) (see Section 6.3.2)
- 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 (see Section 5.2)

*Note: Only Investigators licensed to conduct physical examinations and who are listed on the Delegation of Authority Form are approved to perform physical examinations.
6.1.4 Randomize Subject to Study Medication

Prior to administration of first dose of study drug on Day 1, the Investigator or designee will:

- Determine if subject meets inclusion/exclusion criteria
- Obtain vital signs
  If the subject exhibits uncontrolled hypertension requiring medical intervention or supine SBP > 180 mm Hg or supine DBP > 100 mm Hg at time study medication is scheduled to be administered, do not administer study medication. Subject does not meet exclusion criteria
- Obtain clinical laboratory tests including Hematology panel, Chem 21 panel, and urinalysis (See Section 6.3.2)
  If screening labs are obtained within 7 days prior to first dosing of study medication, then the screening lab may serve as the pre-dose lab
- Obtain blood sample for biomarker assessment (See Section 6.6)
- Obtain urine pregnancy test
  The POC device provided may be used to ensure that a subject’s INR is <2.0 prior to randomization.
  If 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
- Randomize subject to study medication using into the IVRS (See section 5.2)

6.1.5 Treatment Period, Period C

6.1.5.1 Day 1

After randomization, the Investigator or designee will:

- Administer study drug
- Assess for AEs
- Assess changes in concomitant medication use
- Assess for outcomes (death, stroke, systemic embolism, myocardial infarction, bleeding)
6.1.5.2 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.

During all monthly and INR visits, the INR should be monitored by the POC device. If any technical difficulty is experienced with the POC device, the site should first try to resolve the issue with the help desk. If the problem persists, the site should use the contingency procedure for blinded INR tests via the central laboratory. The site should use a special lab kit (IVRS INR Lab Kit) and send a blood sample to the central laboratory. The central laboratory should generate two reports: 1) blinded, for the Investigator informing of sample receipt and 2) unblinded, with INR results for ALMAC. The site will be contacted by ALMAC who will provide an encrypted result which the site will input into the IVRS system. The study blind is therefore preserved.

At the INR visits the Investigator or designee will:

- Perform POC testing for INR
- Obtain pharmacogenomics sample (should be drawn at the Month 2 visit, however, it may be drawn at any scheduled lab collection visit after randomization.)
- 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

6.1.5.3 Procedures for Quarterly Visits (Months 3, 6, 9, 15, 18, 21, 27, 30, 33, 39, 42, 45, 51, 54, and 57)

The Investigator or designee will:

• Obtain vital signs
• Obtain clinical laboratory tests including Hematology and Chem 7 panels (see Section 6.3.2)
• Obtain clinical laboratory tests for assessment of LFT and CK (at the Months 6, 18, 30, 42 and 54 visits only)
• Obtain urine pregnancy tests
• Perform POC testing for INR
• Assess for fractures (at the Months 6, 18, 30, 42 and 54 visits)
• Assess for AEs
• Assess for outcomes (death, stroke, systemic embolism, myocardial infarction, bleeding)
• Assess changes in concomitant medication use
• Collect Study Medication
• Assess Study Medication use
• Dispense Study Medication

6.1.5.4 Procedures for Annual Visits (Months 12, 24, 36 and 48)

The Investigator or designee will:

• Obtain 12 Lead ECG
• Obtain vital signs
• Obtain physical measurements including weight and hip and waist circumference only
• Obtain clinical laboratory tests including Hematology panel, Chem 21 panel, and urinalysis (see Section 6.3.2)
• Obtain urine pregnancy test
• Perform POC testing for INR
• Assess for fractures
• Assess for AEs
• Assess for outcomes (death, stroke, systemic embolism, myocardial infarction, bleeding)
• Assess changes in concomitant medication use
• Collect Study Medication
• Assess Study Medication use
• Dispense Study Medication

6.1.5.5 Procedures for the Final Treatment Visit

The Investigator or designee 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) (see Section 6.3.2)
• 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

* Note: Only Investigators licensed to conduct physical examinations and who are listed on the Delegation of Authority Form are approved to perform physical examinations
6.1.6 Follow-up Period (Period X)

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 448 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 448 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)

The table below describes the details for SAE/SOE collection

<table>
<thead>
<tr>
<th>Situation</th>
<th>Collect SAEs</th>
<th>Collect SOEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>For a subject on study drug</td>
<td>Until end of study</td>
<td>Until end of study</td>
</tr>
<tr>
<td>For subject who has had study drug temporarily interrupted</td>
<td>Until end of study</td>
<td>Until end of study</td>
</tr>
<tr>
<td>For a subject who has study drug permanently discontinued</td>
<td>For 30 days after the last dose of double-blind study drug*</td>
<td>Until end of study</td>
</tr>
</tbody>
</table>

* All SAEs must be followed until resolution. Site personnel may elect, at their discretion, to report SAEs that occur more than 30 days after the last dose of double-blind study drug.

6.2 Study Materials

The following study supplies will be provided

- Adjudication Case Report Forms
- Sample source document worksheets
- Emergency card
In addition Point of Care Devices will be sent to the sites with appropriate documentation

- Pregnancy kits
- Diary Card
- Warfarin Dosing Guidelines

6.3 Safety Assessments

6.3.1 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.

6.3.1.1 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.

For subjects with minor 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. Minor 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)
The management of clinically significant bleeding will in part depend on the randomized treatment assignment (warfarin or apixaban) so unblinding may be necessary (see Section 5.4 on Blinding/Unblinding).

Subjects receiving warfarin should be managed according to the local standard of care. The anticoagulant effects of warfarin will be reflected in the PT/INR and will generally take 3 - 5 days to return to normal. Warfarin can be reversed more quickly by giving oral or intravenous vitamin K, and/or with fresh frozen plasma (FFP, 2 units IV every 6 hours).

There is no reversal agent for apixaban. Given its half-life (12 - 15 hours), however, the anticoagulant effect of apixaban abates in 24 - 48 hours. Subjects receiving apixaban with clinically significant bleeding that does not respond to local measures may be treated with FFP (2 units IV every 6 hours) for 24 - 48 hours or until the bleeding has stopped.

For subjects with life threatening bleeding and significant thrombocytopenia or those receiving antiplatelet drugs, transfusion of platelets can be considered. There are few randomized clinical trials of recombinant Factor VIIa (rFVIIa, NovoSeven®) and warfarin induced hemorrhage, and there are pro-thrombotic risks. A recent phase 3 clinical trial employing rFVIIA for treatment of acute spontaneous intracerebral hemorrhage yielded disappointing results (Factor Seven for Acute Hemorrhagic Stroke (FAST) Trial, in press). There is no experience with rFVIIa and apixaban.

Some experts have recommended the use of prothrombin complex concentrate (PCC, also referred to as Factor IX concentrate) for reversal of warfarin associated coagulopathy and hemorrhage. There are few randomized clinical trials in this area, but observational studies and some guidelines are cited in support of this approach. There are a variety of PCC formulations available, they differ in their concentration of clotting factors (II, VII, IX and X). Dosing depends on body weight, the formulation of PCC employed, the degree of anticoagulation (INR), the clinical picture and whether concomitant FFP is also administered. Thrombotic events have been reported with PCC use. Given the complexity of the dosing and the risks involved, it is recommended that the decision to employ a PCC for warfarin associated hemorrhage be made by an experienced clinician with careful evaluation of the risks and benefits. There is no data regarding the use of PCC for treatment of apixaban related hemorrhage.
6.3.2 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 as outlined in Section 6.1. A central laboratory will perform the analyses 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:

Hematology Profile:
- Hematocrit
- Hemoglobin
- Red Blood Cell Count
- MCV
- MCHC
- MCH
- White Blood Cell Count
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils
- Neutrophils
- Platelet Count

Chem 21 Panel:
- Albumin
- BUN (Urea)
- Calcium
- Chloride
- Bicarbonate
- CK
- Creatinine
- Glucose
- Potassium
• Sodium
• ALP
• ALT
• AST
• Direct Bilirubin
• Total Bilirubin
• GGT
• Phosphate
• Total Protein
• Uric acid (Urate)
• Total Cholesterol
• LDH

Chem 7 Panel:
• BUN (Urea)
• Chloride
• Bicarbonate
• Creatinine
• Glucose
• Potassium
• Sodium

Coagulation Profile:
• INR
• aPTT

Urinalysis:
• Protein
• Glucose
• Leukocyte Esterase
• Nitrite
• Blood
• pH
• Ketones
• Specific Gravity
• Bilirubin
• Urobilinogen

Microscopic Urinalysis:
• RBC
• WBC
• Casts
• Crystals
• Epithelial Cells
• Yeast
• Bacteria

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. Samples for measurement of biomarkers may be drawn at the same time as scheduled collections for clinical laboratory tests prior to dosing on Day 1.

6.3.2.1 Pregnancy Tests

A pregnancy test (for WOCBP, see Section 6.1.4) 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
6.3.2.2 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:

\[
Cl_{cr} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{(weight in kg)} \times 0.85 \text{ for females}}{\text{serum creatinine (mg/dL)} \times 72}
\]

6.3.2.3 Treatment Guidelines for Jaundice, Elevated LFTs

The following guidelines are intended to identify and manage subjects with potential hepatotoxicity. Specific laboratory test criteria and instructions for further follow-up are provided.

If at any time during the treatment period a subject’s liver function test (LFT) results show:

- An isolated elevation of either ALT ≥ 3 x ULN OR a total bilirubin ≥ 2 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, CK within one week
- An elevation of BOTH ALT ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, CK as soon as possible (i.e., within ≤ 3 days)

If the repeat tests indicate:

- ALT < 3 x ULN and total bilirubin < 2 x ULN, study medication may continue
- ALT ≥ 3x ULN but < 5 x ULN and total bilirubin < 2 x ULN study medication may continue but repeat LFTs weekly until ALT < 1.5 x ULN or to baseline if subjects entered the study with an ALT ≥ 1.5 x ULN
- If the repeat ALT ≥ 3x ULN AND the total bilirubin is ≥ 2 x ULN, study medication must be discontinued unless, in consultation with the BMS Medical Monitor/Trial Helpline, an alternative causative factor (e.g., Gilbert’s syndrome) is identified.
Study medication must be discontinued if:

- Clinical jaundice is present for a subject at any time

OR

- If ALT ≥ 5 x ULN on any two consecutive occasions

OR

- Total bilirubin ≥ 2.0 x ULN on any two consecutive occasions in the absence of an alternative causative factor [e.g., Gilbert’s syndrome] is identified

All subjects with an ALT ≥3x ULN or total bilirubin ≥ 2x ULN will be followed weekly until ALT and total bilirubin return to < 1.5x ULN or to baseline if subjects entered the study with an ALT ≥ 1.5 xULN.

If study medication is discontinued due to elevated ALT or bilirubin, as defined above, inform the Medical Monitor and perform the following:

- Hepatitis screen (anti-HAV, HbsAg, anti-HBc, anti-HBs and anti-HCV)
- Abdominal ultrasound, including liver and hepatobiliary system

### 6.3.3 Vital Signs

Vital signs (blood pressure and heart rate) will be recorded during the screening visit, prior to dosing on Day 1, and at the quarterly, annual and end of treatment period visits.

### 6.3.4 Electrocardiograms

A 12-lead ECG will be recorded at screening and at the annual and end of treatment period visits.

### 6.3.5 Physical Examinations

Targeted physical examinations will be performed at the screening visit.
6.3.6 Physical Measurements

Physical measurements, including height, weight, hip circumference, and waist circumference will be measured at the screening visit. Weight, hip circumference, and waist circumference will be measured at the annual visits during the treatment period.

6.3.7 Fracture Assessments

History of fractures will be obtained at the screening visit. Details of new fractures occurring during the treatment period will be recorded every 6 months during the treatment period and at the end of treatment visit.

6.3.8 Concomitant Medications

At the screening visit, medications that subjects have used in the past 30 days will be recorded. At the Day 1, Month 1, quarterly, annual and end of treatment visits, changes in concomitant medications since the last data collection will also be recorded.

6.4 Efficacy Assessments

6.4.1 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.

### 6.4.2 Secondary Efficacy Assessments

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.

- a) 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).

- b) 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.

### 6.4.2.1 Treatment Guidelines for ACS, Stroke, Systemic Embolism

If the subject experiences acute coronary syndrome (ACS), stroke, or systemic embolism the subject should be managed at the discretion of the treating physician (see Section 5.4.1.2 for general guidance). No laboratory samples are required to be sent to the Central Laboratory. The appropriate SAE and CRF pages must be completed.

### 6.5 Pharmacokinetic Assessments

The pharmacokinetics of apixaban in this subject population will be assessed in an optional substudy. In this substudy, blood sample(s) will be collected to assess apixaban plasma concentrations. A detailed description of sample collection, processing, storage, and shipping procedures will be specified in an Amendment for sites that participate in this substudy.

### 6.6 Pharmacodynamics Assessments

Selected biomarkers of hemostasis, inflammation, platelet activation, endothelial dysfunction, and/or cardiovascular disease will be measured on Day 1 prior to first dose. The pharmacodynamics of apixaban and warfarin will be assessed at one or more times during treatment in subjects participating in an optional substudy. Blood samples will be analyzed for biomarkers such as, but not limited to, D-dimer, hs-CRP, sCD40L, ADMA, and NTproBNP. A detailed description of sample collection, processing, storage, and shipping procedures will be specified in an Amendment for sites that participate in this substudy.
6.7 Pharmacogenomics Assessments

See Amendment 01 (Pharmacogenetics Blood Sample Amendment) for details.

6.8 Outcomes Research Assessments

An optional within-trial economic analysis will be conducted in this study. The purpose of this analysis is to demonstrate the effectiveness of apixaban in reducing stroke (hemorrhagic, ischemic or of unspecified type), systemic embolism and bleeding-related healthcare resource utilization and costs compared to warfarin.

The source of cost information will be healthcare resource utilization incurred in the clinical trial. Hospitalizations, emergency room visits, outsubject visits, medical procedures and medications will be captured on the case report form. Costs beyond the trial period will be extrapolated from the trial.

6.9 Other Assessments

None.

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 (see note below for exceptions)
- 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 [see Section 7.6])
- 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.)

For reporting purposes, BMS also considers the occurrence of pregnancy (see Section 7.6), overdose (regardless of association with an AE), and cancer as important medical events. An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
7.1.2 Nonserious Adverse Events

All AEs that are not classified as serious.

7.1.3 Events of Special Interest

The clinical events described below have been identified as events of special interest. In addition to appropriate reporting as an AE or SAE, detailed information on these events will be collected.

7.1.3.1 Thrombocytopenia

Determined by the DMC based on evidence in a clinical dossier (e.g., hospital records). In addition, the DMC determines whether the event is associated with a disseminated thrombosis syndrome. Thrombocytopenia is defined as a decline in platelet count to < 100,000/mm$^3$ for subjects with a baseline value > 150,000/mm$^3$ or a > 50% decline if the baseline value is ≤ 150,000/mm$^3$.

7.1.3.2 Elevated liver function tests

Liver function tests will be performed at pre-specified time points (see Section 6.1) and at unscheduled times according to standard subject care. Follow-up testing and treatment guidelines are provided for jaundice and elevated LFTs (see Section 6.3.2.3).

7.1.3.3 Neuropathy

All AE reports will be compared to a list of terms from the Medical Dictionary for Regulatory Activities (MedDRA) that are suggestive of possible neuropathies or other neurological events. AEs matching any of these terms that persist for at least 7 days or result in a neurology consultation will be followed by collection of additional specific information on specialized case report forms for these type of events. Neurological consultations will be recommended for any SAEs matching the list of terms suggestive of possible neuropathies or other neurological events.
7.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following categories and definitions of intensity as determined by a physician should be used for all BMS clinical study AEs:

- **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)** - Debilitating, significantly incapacitates subject despite symptomatic therapy

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for all BMS clinical study AEs:

- **Certain**: There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
- **Probable**: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- **Possible**: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- **Not likely**: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- **Not related**: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between noninvestigational product, concurrent disease, or circumstance and the AE.

7.3 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.

### 7.3.1 Serious Adverse Events

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. (See table 6.1.7 SAE/SOE Collection). 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.

All SAEs must be reported within 24 hours by confirmed facsimile transmission (fax) or scanned and reported via electronic mail. If only limited information is initially available, follow-up reports are required. (Note: follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions which require additional telephone reporting. The SAE electronic CRF in the electronic data capture tool should not be used.

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.
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.

**SAE FACSIMILE TRANSMISSION:**

For all sites; except China, Israel, Russia and Ukraine (see Appendix 2 for special instructions):

**Central Facsimile Stations:**
- **Europe and Asia Pacific:** +44 1223 374102
- **Latin America (including Central and South America, and Puerto Rico):** +55 11 4504 4802
- **North America:** 1-888-529-3580

**SAE Email Addresses:**
- **Europe and Asia Pacific:** emeasiasafetycentral.sm@ppdi.com
- **Latin America (including Central and South America and Puerto Rico):** latsafety@ppdi.com
- **North America:** rtpsafty@ppdi.com

**SAE Telephone Contact/24 Hour Medical Monitor Contact:**
- **Europe and Asia Pacific:** +44 1223 374 240
- **Latin America (including Central and South America and Puerto Rico):** +55 11 4504 4801
- **North America:** 1-888-483-7729

### 7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are unexpected (i.e., not previously described in the Investigator Brochure), and certainly, probably, or possibly related to the investigational product or that could be associated
with the study procedures. This notification will be in the form of an expedited safety report (ESR).

Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information. Suspected serious adverse reactions shall be reported to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited cases or in aggregate reports).

Any unexpected study outcome event that results in death will be reported as an ESR. However, non-fatal SAEs which are study outcomes will not be reported by BMS as ESRs to study Investigators, health authorities, or IRB/EC. Events that will not be reported by BMS as an ESR include:

- ischemic stroke
- hemorrhagic stroke
- stroke of unspecified type
- systemic embolism
- major bleeding events
- myocardial infarction

An independent DMC (See Section 4.1.4) will review on a regular basis, and whenever necessary, efficacy and safety data from the ongoing trial, including the above events and all SAEs reported to the Sponsor.

### 7.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.
If an ongoing AE changes in its intensity or in its perceived relationship to investigational product, a new AE entry for the event should be completed. Adverse events should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.3.1). Follow-up is also required for AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF (paper or electronic).

### 7.4 Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the CRF, or be submitted electronically from a central laboratory. In addition, the following laboratory abnormalities should also be captured on the nonserious AE electronic CRF page or SAE paper CRF page; due to technology limitations, some sites may continue to use paper nonserious AE page(s) as appropriate:

- Any laboratory test result that is clinically relevant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have investigational product discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

### 7.5 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 7.3.1 for reporting details.)
7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized (See Section 4.2.2 for definition of WOCBP).

Before enrolling WOCBP in this clinical study, investigators must review the guideline about study participation for WOCBP which can be found on the training website. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factor(s) for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test within 48 hours as specified in Section 6.1.4 prior to receiving investigational product. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive investigational product and must not be enrolled in the study.

Pregnancy testing must also be performed throughout the study as specified in Section 6.3.2.1 (see flow chart/time and events schedule) and the results of all pregnancy tests (positive or negative) recorded on the case report form.
In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

### 7.6.2 Reporting of Pregnancy

If, following initiation of investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Exceptions to investigational product discontinuation may be considered for life-threatening conditions only after consultation with the BMS Medical Monitor or as otherwise specified in this protocol. The Investigator must immediately notify the BMS Medical Monitor of this event, record the pregnancy on the Pregnancy Surveillance Form. Pregnancy Surveillance Form Part 1 must be completed when a pregnancy has been identified. Part 2 of this form must be completed when the pregnancy outcome is known. Forward these forms to BMS according to SAE reporting procedures as described in Section 7.3.1.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to BMS, on the appropriate BMS Pregnancy Surveillance Forms (Parts 1 and 2), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Follow up information regarding the course of the pregnancy, including perinatal and neonatal outcome must be reported on the Pregnancy Supplemental Form. Infants should be followed for a minimum of 8 weeks. Part 1 must be completed when the pregnancy is identified and Part 2 is completed when the pregnancy outcome is known.

The reporting of a female partner’s pregnancy may be requested if animal toxicology studies show concern for reproductive risk.
7.7 Other Safety Considerations

Any significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate nonserious AE page of the CRF (paper or electronic) or SAE paper CRF page.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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. This objective will be addressed by testing the following hypothesis:

\[ H_0 : \text{RR} \geq \Delta \]

versus

\[ H_1 : \text{RR} < \Delta, \]

where RR represents the risk of apixaban relative to warfarin. 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. These studies are described by J. Lawrence (FDA Statistical Reviewer for Exanta NDA) along with the details of a meta-analysis for the studies. Following that methodology a 64% relative risk reduction was identified in favor of warfarin for the primary outcome of this trial (lower bound of two-sided 95% CI for relative risk reduction = 47%). This allowed us to calculate the excess risk due to placebo versus warfarin at 2.78 (lower bound of two-sided 95% CI for this excess risk =1.88). In order to show that apixaban preserves at least some of the warfarin benefit, one must then show that the upper bound of a two-sided CI for the relative risk of apixaban versus warfarin does not exceed 1.88. However, it is more clinically relevant and conventional to choose a more stringent margin of non-inferiority and we have designed this trial with 90%
power to show that apixaban maintains at least half of a conservative estimate of the historical benefit of warfarin relative to placebo. To do this, the upper limit of a two-sided CI for the relative risk of apixaban versus warfarin must be less than 1.44.

The apixaban indication for prevention of stroke in AF subjects may be supported by this single pivotal trial. Different regulatory agencies have different requirements for such a regulatory submission. Some agencies require a more stringent control of the type I error (one-sided 0.005 level rather than one-sided 0.025 level) in the presence of a single registrational trial. Others require a more stringent non-inferiority margin (1.38 rather than 1.44). Therefore,

(A) in regulatory regions requiring a more stringent non-inferiority margin, the non-inferiority of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 95% CI for RR is less than 1.38

(B) in regulatory regions requiring a more stringent control of the type I error, the non-inferiority of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.

The number of events required to achieve 90% power and meet the criteria described in (A) is lower than the number of events required to achieve 90% power and meet the criteria described in (B). This study is sized to meet the more stringent criterion. With 448 subjects with confirmed strokes or systemic emboli, the study will have at least 90% power to meet both regulatory definitions of non-inferiority described above. With an average 2.1 years follow-up and assuming a stroke rate of 1.20 per hundred subject-years, a total of approximately 18,000 randomized subjects allocated in a 1:1 ratio to the apixaban or warfarin group will be needed to achieve the desired power. These calculations assume an incidence of 1% loss to follow-up.

8.2 Populations for Analyses

The primary efficacy data set will consist of all randomized subjects. Subjects will be categorized to the group to which they were assigned by the IVRS, regardless of the treatment actually received. Only events confirmed by the adjudication committee will be included in the analyses. Each subject’s first confirmed event occurring between randomization and the study’s efficacy cut-off date will be used.
A secondary data set, the evaluable subject data set, will exclude data from subjects with protocol deviations expected to affect the primary efficacy endpoint. Such protocol deviations will be pre-specified in the statistical analysis plan prior to unblinding the data base.

For the primary efficacy endpoint, analyses will be performed using the evaluable subject data set as well as the primary efficacy data set. For the secondary efficacy endpoints, analyses will be performed using the primary efficacy data set.

For the primary and secondary safety endpoints, analyses will be performed using data from all randomized subjects who receive any study drug.

8.3 Endpoint Definitions

8.3.1 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.

8.3.2 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.

8.4 Analyses

8.4.1 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.

The summaries will be tabulated for all randomized subjects and also for subjects included in the evaluable subject dataset.
8.4.2 Safety Analyses

The term “treatment period” refers to the period between the first administration of study drug and two days after the last administration of study drug. This period will be the basis for the summaries of safety.

Primary Safety Analyses

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 investigative site and 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 Analyses

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.

Changes from baseline in laboratory parameters will be summarized at each measurement time point by treatment group.

8.4.3 Efficacy Analyses

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 example, 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 Analyses**

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. As noted in Section 8.1 different agencies have different regulatory standards for demonstrating non-inferiority:

- in regulatory regions for which the criterion requires testing at one-sided 0.005 significance level and a non-inferiority margin of 1.44, non-inferiority will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.
- in regulatory regions for which the criterion requires testing at one-sided 0.025 significance level and a non-inferiority margin of 1.38, non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI for RR is less than 1.38.

Tests using each non-inferiority margin will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin / VKA status (experienced, naïve). Investigative sites will be pooled to the geographic region level.

A confirmatory analysis will be performed using a Cox model stratified by investigative site and prior warfarin / VKA status and including as covariates treatment group, history
of stroke, TIA or non-systemic embolus, history of diabetes mellitus, on treatment for systemic hypertension, history of myocardial infarction, and history of coronary heart failure.

Event rates for the primary efficacy endpoint will also be summarized by treatment group and demographic and baseline characteristics, including geographic region, age, gender, race, body mass index, prior warfarin/VKA status (experienced, naïve), risk factor type, number of risk factors, smoking history, baseline medications, atrial fibrillation type and onset.

**Key Secondary Analyses**

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

NI for the primary efficacy endpoint will be assessed first (refer to Section 5 for NI margins and significance levels associated with this assessment). If non-inferiority (using a NI margin of 1.38) is demonstrated then:

a) superiority for the primary efficacy endpoint will be tested

b) if superiority for the primary efficacy endpoint is
   i) not demonstrated, then stop
   ii) demonstrated, then superiority for major bleeding will be tested

c) if superiority for major bleeding is
   i) not demonstrated, then stop
   ii) demonstrated, then superiority for all cause death will be tested.

All tests will be performed at the one-sided $\alpha = 0.025$ significance level. The procedure to control the type I error across potential regulatory claims will be documented in the statistical analysis plan.

**Other Secondary Efficacy Analysis**

Event rates for the following secondary efficacy endpoints will be summarized by treatment group:
• 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 and major bleeding in warfarin naive subjects
• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, major bleeding
• composite of stroke (ischemic, hemorrhagic, or of unspecified type), major bleeding, all cause death
• composite of stroke (ischemic, hemorrhagic, or of unspecified type), systemic embolism, all cause death
• composite of stroke (ischemic, hemorrhagic, or of unspecified type), myocardial infarction, all cause death.

Point estimates and two-sided 95% CIs for RR will be constructed for each of these secondary efficacy endpoints using the methods described for the primary efficacy endpoint and p-values will also be provided.

8.4.4 Pharmacokinetic Analyses

Plans for analyzing apixaban plasma concentrations will be provided in a separate amendment.

8.4.5 Pharmacodynamic Analyses

Plans for analyzing biomarker data and pharmacodynamic responses will be provided in a separate amendment.

8.4.6 Pharmacogenomic Analyses

See Amendment 01 (Pharmacogenetics Blood Sample Amendment) for details.
8.4.7 Outcomes Research Analyses

Mean healthcare costs associated with study outcomes will be compared between the two arms, and the 95% CIs will be constructed. A multivariate regression model will also be used to compare mean costs adjusting for covariates.

8.5 Interim Analyses

A formal interim analysis will be performed once 50% of the primary efficacy endpoint events have been confirmed by the CEC. 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. As outlined in the DMC charter, the DMC could recommend stopping the study if the one-sided p-value associated with the superiority test for the primary efficacy endpoint is < 0.0001. 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.

8.6 Plan for Long Term Follow-up

After the visit/follow-up call that is to occur approximately 30 days after 448 primary efficacy events have been adjudicated, there will be the opportunity for long-term “passive” follow-up. Where feasible, mortality follow-up using national death indices for a 5 year period may be conducted.

8.7 Publications and Presentations

The Executive Committee will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study (design, baseline data, mortality and safety data) and approved sub-study, ancillary analyses within a timely fashion after completion of the study. A set of publication guidelines will be created.
Manuscripts for publication will be drafted by the Executive Steering Committee and will be circulated for input from the overall Steering Committee prior to submission.

Other manuscript(s) for publication by the Steering Committee and/or investigators will be encouraged and supported as appropriate. These materials must be submitted to the Sponsors and the Executive Steering Committee for review and comment prior to publication, public dissemination or review.

9 ADMINISTRATIVE SECTION

9.1 Compliance

9.1.1 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.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the
amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY BMS PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, study documentation, informed consent, and enrolling WOCBP.

In addition, each individual making entries and/or corrections on electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

For electronic CRFs, corrections are made through the BMS electronic data capture tool, which generates an automated audit trail including date and timestamp, full name of the person making the correction and original entry. The system also prompts the user to document reason for change which is also maintained in the audit trail.
Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

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.

All sites within this study will use electronic data capability to submit study data to BMS. Electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on paper SAE forms and Pregnancy Surveillance Forms. Paper CRFs must be completed legibly in ink. Electronic data transfer is acceptable. Subjects are to be identified by initials, birth date, and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.
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.

For paper CRFs, a correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

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.

9.2.2 Investigational Product Records

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number and use date or expiry date
- dates and initials of person responsible for each investigational product inventory entry/movement
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (e.g., lost, wasted, broken)
- amount returned to the sponsor
• amount destroyed at study site, if applicable
• retain samples sent to third party for bioavailability/bioequivalence, if applicable

The sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

9.3 Return and Destruction of Investigational Product

9.3.1 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMS, if not authorized by BMS to be destroyed at the site.

All investigational product returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original containers (e.g., subject kits that have clinical labels attached). Empty containers should not be returned to BMS. It is the Investigator’s responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

9.3.2 Destruction of Investigational Product

If investigational products are to be destroyed on site, it is the Investigator’s responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by BMS, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.
## 10 Glossary of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Expected Adverse Event</td>
<td>An event that is described or mentioned in the applicable (current version) or the prescribing information for the drug (e.g., Investigator Brochure for an investigational product, approved local label for a marketed product).</td>
</tr>
<tr>
<td>Investigational Product</td>
<td>An investigational product, also known as investigational medicinal product in some regions, is:</td>
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<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Noninvestigational Product</td>
<td>Support, escape (rescue) or diagnostic medications (marketed form), concomitant medications</td>
</tr>
</tbody>
</table>
## 11 LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>aPTT</td>
<td>activated partial thromboplastin time</td>
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<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>AT</td>
<td>anti-thrombin</td>
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<tr>
<td>BID</td>
<td>twice-daily</td>
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<tr>
<td>BMS</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
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<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CK</td>
<td>creatine kinase</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<td>------------------------------------------------</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CRF</td>
<td>case report form</td>
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<tr>
<td>CSR</td>
<td>clinical study report</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>D/C</td>
<td>discontinuation</td>
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<tr>
<td>D-dimer</td>
<td>D fragment released by plasmin degradation of fibrin</td>
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<tr>
<td>Df</td>
<td>degree of freedom</td>
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<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>EOT</td>
<td>End of treatment</td>
</tr>
<tr>
<td>F1.2</td>
<td>prothrombin fragment 1.2</td>
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<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>FTV</td>
<td>Final treatment visit</td>
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<tr>
<td>FXa</td>
<td>Factor Xa</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<td>------------------------------------------------</td>
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<tr>
<td>HCG</td>
<td>human chorionic gonadotropin</td>
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<td>Hct</td>
<td>hematocrit</td>
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<tr>
<td>Hgb</td>
<td>hemoglobin</td>
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<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IEC</td>
<td>International Ethics Committee</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>IU</td>
<td>international units</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function tests</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
</tr>
<tr>
<td>PO</td>
<td>by mouth</td>
</tr>
<tr>
<td>POC</td>
<td>point of care</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>QD</td>
<td>once-daily</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell count</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>RRR</td>
<td>relative risk reduction</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SE</td>
<td>systemic embolism</td>
</tr>
<tr>
<td>SD</td>
<td>Switch Day</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>VKA</td>
<td>vitamin K antagonist</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>WOCBP</td>
<td>women of childbearing potential</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki. If the investigator makes changes to the informed consent form sample, BMS will ensure all required elements and local regulatory and legal requirements are met.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

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. (In the event that
the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, e.g., for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.3 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.
In circumstances where a subject’s only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject’s informed consent.

1.1.4 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject’s rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.
During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.
APPENDIX 2 SAE NOTIFICATION INFORMATION FOR SITES LOCATED OUTSIDE THE US

All SAEs must be reported within 24 hours by confirmed facsimile transmission (fax) or scanned and reported via electronic mail. (See Section 7.3.1 in the protocol body).

**China**
Medical Monitor: Wang Bei, MD  
Sino-American Shanghai Squibb Pharmaceuticals Ltd.  
6 Floor, Fuxing Plaza, Yandang Road, Shanghai 200020  
Telephone (office): 86-21-23218412  
24 Hour: 86-13764311697

Alternate Contact:  
Fiona Liu  
Office: 86-21-23218364  
24 Hour: 86-13761317242

**SAE Facsimile Number: 86-21-53860383**

**Israel**
Stephen Levenstein, MD  
GCP Clinical Studies Ltd.  
22 Hamelacha Street  
P.O. Box 11372  
Rosh HáAyin, 48091  
Telephone (office): 972-3-900-2003  
24 Hour Number: 972-544-772853

**SAE Facsimile Number: 972-3-902-7138**

**Russia**
Natalia Berzak, MD, PhD  
Clinstar Europe  
Telephone (office): 7 495 793 0080 Ext. 1213  
24 hour number: 7 916 886 90 75

**SAE Facsimile Number: 7495 7380083**  
**SAE Email: bms_sae@clinstar.com**

**Ukraine**
Yevgen Shaydrov, MD  
Clinstar Ukraine, LLC  
Telephone (office): 38044 594 5555 Ext. 4173  
24 Hour: 38 050 446 52 25

**SAE Facsimile Number: 7 495 7390083**  
**SAE Email: bms_sae@clinstar.com**

Revised Protocol No.: 04  
Date: 04-Aug-2010

Approved v8.0 930018272 6.0
APPENDIX 3  COUMADIN PACKAGE INSERT

PDR® entry for

COUMADIN® TABLETS (Bristol-Myers Squibb)  
(Warfarin Sodium Tablets, USP) Crystalline
COUMADIN® FOR INJECTION  
(Warfarin Sodium for Injection, USP)  
ANTICOAGULANT
Rx only

1.1.1.1  DESCRIPTION

COUMADIN (crystalline warfarin sodium) is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors. Chemically, it is 3-((alpha)-acetonylbenzyl)-4-hydroxycoumarin and is a racemic mixture of the R- and S-enantiomers. Crystalline warfarin sodium is an isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin. Its empirical formula is C_{19}H_{15}NaO_{4}, and its structural formula may be represented by the following:

![Structural formula of warfarin sodium]

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder, is discolored by light and is very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

COUMADIN Tablets for oral use also contain:

<table>
<thead>
<tr>
<th>All strengths:</th>
<th>Lactose, starch and magnesium stearate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg:</td>
<td>D&amp;C Red No. 6 Barium Lake</td>
</tr>
<tr>
<td>2 mg:</td>
<td>FD&amp;C Blue No. 2 Aluminum Lake and FD&amp;C Red No. 40 Aluminum Lake</td>
</tr>
<tr>
<td>2-1/2 mg:</td>
<td>D&amp;C Yellow No. 10 Aluminum Lake and FD&amp;C Blue No. 1 Aluminum Lake</td>
</tr>
<tr>
<td>3 mg:</td>
<td>FD&amp;C Yellow No. 6 Aluminum Lake, FD&amp;C Blue No. 2 Aluminum Lake and</td>
</tr>
</tbody>
</table>

Revised Protocol No.: 04  
Date: 04-Aug-2010
COUMADIN for Injection is supplied as a sterile, lyophilized powder, which, after reconstitution with 2.7 mL sterile Water for Injection, contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Sodium</td>
<td>2 mg/mL</td>
</tr>
<tr>
<td>Sodium Phosphate, Dibasic, Heptahydrate</td>
<td>4.98 mg/mL</td>
</tr>
<tr>
<td>Sodium Phosphate, Monobasic, Monohydrate</td>
<td>0.194 mg/mL</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.1 mg/mL</td>
</tr>
<tr>
<td>Mannitol</td>
<td>38.0 mg/mL</td>
</tr>
<tr>
<td>Sodium Hydroxide, as needed for pH adjustment to</td>
<td>8.1 to 8.3</td>
</tr>
</tbody>
</table>

1.1.1.2 CLINICAL PHARMACOLOGY

COUMADIN and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II - 60 hours, VII - 4-6 hours, IX - 24 hours, and X - 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively. The resultant in vivo effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of (gamma)-carboxyglutamic acid residues in the proteins which are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K₁ epoxide. The degree of depression is dependent upon the dosage administered. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anticoagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of COUMADIN
may become more pronounced as effects of daily maintenance doses overlap. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications which may result in serious and possibly fatal sequelae.

**Pharmacokinetics:** COUMADIN is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

**Absorption:** COUMADIN is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

**Distribution:** There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 liter/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model, and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see **WARNINGS: Lactation**). Approximately 99% of the drug is bound to plasma proteins.

**Metabolism:** The elimination of warfarin is almost entirely by metabolism. COUMADIN is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine; and to a lesser extent into the bile. The metabolites of warfarin that have been identified include dehydrowarfarin, two diastereoisomer alcohols, 4', 6', 7', 8- and 10-hydroxywarfarin. The cytochrome P-450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of human liver P-450 which modulates the in vivo anticoagulant activity of warfarin.

**Excretion:** The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours, with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

**Elderly:** Patients 60 years or older appear to exhibit greater than expected prothrombin time (PT)/International Normalized Ratio (INR) response to the
anticoagulant effects of warfarin. The cause of the increased sensitivity to the anticoagulant effects of warfarin in this age group is unknown. This increased anticoagulant effect from warfarin may be due to a combination of pharmacokinetic and pharmacodynamic factors. Racemic warfarin clearance may be unchanged or reduced with increasing age. Limited information suggests there is no difference in the clearance of S-warfarin in the elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly as compared to the young. Therefore, as patient age increases, a lower dose of warfarin is usually required to produce a therapeutic level of anticoagulation.

**Asians:** Asian patients may require lower initiation and maintenance doses of warfarin. One non-controlled study conducted in 151 Chinese outpatients reported a mean daily warfarin requirement of $3.3 \pm 1.4 \text{ mg}$ to achieve an INR of 2 to 2.5. These patients were stabilized on warfarin for various indications. Patient age was the most important determinant of warfarin requirement in Chinese patients with a progressively lower warfarin requirement with increasing age.

**Renal Dysfunction:** Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

**Hepatic Dysfunction:** Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

The administration of COUMADIN (Warfarin Sodium) via the intravenous (IV) route should provide the patient with the same concentration of an equal oral dose, but maximum plasma concentration will be reached earlier. However, the full anticoagulant effect of a dose of warfarin may not be achieved until 72-96 hours after dosing, indicating that the administration of IV COUMADIN should not provide any increased biological effect or earlier onset of action.

### 1.1.3 Clinical Trials

**Atrial Fibrillation (AF):** In five prospective randomized controlled clinical trials involving 3711 patients with non-rheumatic AF, warfarin significantly reduced the risk of systemic thromboembolism including stroke (See Table 1). The risk reduction ranged from 60% to 86% in all except one trial (CAFA: 45%) which stopped early due to published positive results from two of these trials. The incidence of major bleeding in these trials ranged from 0.6 to 2.7% (See Table 1). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available.
TABLE 1. Clinical Studies of Warfarin in Non-Rheumatic AF Patients *

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin-Treated Patients</th>
<th>Control Patients</th>
<th>PT Ratio</th>
<th>INR</th>
<th>% Risk Reduction</th>
<th>p-value</th>
<th>% Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>335</td>
<td>336</td>
<td>1.5-2.0</td>
<td>2.8-4.2</td>
<td>60</td>
<td>0.027</td>
<td>0.6</td>
</tr>
<tr>
<td>SPAF</td>
<td>210</td>
<td>211</td>
<td>1.3-1.8</td>
<td>2.0-4.5</td>
<td>67</td>
<td>0.01</td>
<td>1.9</td>
</tr>
<tr>
<td>BAATAF</td>
<td>212</td>
<td>208</td>
<td>1.2-1.5</td>
<td>1.5-2.7</td>
<td>86</td>
<td>&lt;0.05</td>
<td>0.9</td>
</tr>
<tr>
<td>CAFA</td>
<td>187</td>
<td>191</td>
<td>1.3-1.6</td>
<td>2.0-3.0</td>
<td>45</td>
<td>0.25</td>
<td>2.7</td>
</tr>
<tr>
<td>SPINAF</td>
<td>260</td>
<td>265</td>
<td>1.2-1.5</td>
<td>1.4-2.8</td>
<td>79</td>
<td>0.001</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*All study results of warfarin vs. control are based on intention-to-treat analysis and include ischemic stroke and systemic thromboembolism, excluding hemorrhage and transient ischemic attacks.

**Myocardial Infarction:** WARIS (The Warfarin Re-Infarction Study) was a double-blind, randomized study of 1214 patients 2 to 4 weeks post-infarction treated with warfarin to a target INR of 2.8 to 4.8. [But note that a lower INR was achieved and increased bleeding was associated with INR’s above 4.0; (see DOSAGE AND ADMINISTRATION )]. The primary endpoint was a combination of total mortality and recurrent infarction. A secondary endpoint of cerebrovascular events was assessed. Mean follow-up of the patients was 37 months. The results for each endpoint separately, including an analysis of vascular death, are provided in the following table:

TABLE 2

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin (N=607)</th>
<th>Placebo (N=607)</th>
<th>RR (95% CI)</th>
<th>% Risk Reduction (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patient Years of Follow-up</td>
<td>2018</td>
<td>1944</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Mortality Vascular Death</td>
<td>94 (4.7/100 py)</td>
<td>123 (6.3/100 py)</td>
<td>0.76 (0.60, 0.97)</td>
<td>24 (p=0.030)</td>
</tr>
<tr>
<td></td>
<td>82 (4.1/100 py)</td>
<td>105 (5.4/100 py)</td>
<td>0.78 (0.60, 1.02)</td>
<td>22 (p=0.068)</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>82 (4.1/100 py)</td>
<td>124 (6.4/100 py)</td>
<td>0.66 (0.51, 0.85)</td>
<td>34 (p=0.001)</td>
</tr>
<tr>
<td>Cerebrovascular Event</td>
<td>20 (1.0/100 py)</td>
<td>44 (2.3/100 py)</td>
<td>0.46 (0.28, 0.75)</td>
<td>54 (p=0.002)</td>
</tr>
</tbody>
</table>

RR=Relative risk; Risk reduction=(1 - RR); CI=Confidence interval; MI=Myocardial infarction; py=patient years

**Mechanical and Bioprosthetic Heart Valves:** In a prospective, randomized, open label, positive-controlled study (Mok et al, 1985) in 254 patients, the thromboembolic-free interval was found to be significantly greater in patients with mechanical prosthetic heart valves treated with warfarin alone compared with dipyridamole-aspirin (p<0.005) and pentoxifylline-aspirin (p<0.05) treated patients. Rates of thromboembolic events in these groups were 2.2, 8.6, and 7.9/100 patient
years, respectively. Major bleeding rates were 2.5, 0.0, and 0.9/100 patient years, respectively.

In a prospective, open label, clinical trial (Saour et al, 1990) comparing moderate (INR 2.65) vs. high intensity (INR 9.0) warfarin therapies in 258 patients with mechanical prosthetic heart valves, thromboembolism occurred with similar frequency in the two groups (4.0 and 3.7 events/100 patient years, respectively). Major bleeding was more common in the high intensity group (2.1 events/100 patient years) vs. 0.95 events/100 patient years in the moderate intensity group.

In a randomized trial (Turpie et al, 1988) in 210 patients comparing two intensities of warfarin therapy (INR 2.0-2.25 vs. INR 2.5-4.0) for a three-month period following tissue heart valve replacement, thromboembolism occurred with similar frequency in the two groups (major embolic events 2.0% vs. 1.9%, respectively and minor embolic events 10.8% vs. 10.2%, respectively). Major bleeding complications were more frequent with the higher intensity (major hemorrhages 4.6%) vs. none in the lower intensity.

1.1.1.4 INDICATIONS AND USAGE

COUMADIN is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.

COUMADIN is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.

COUMADIN is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

1.1.1.5 CONTRAINDICATIONS

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

Pregnancy: COUMADIN is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the
corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia, characterized by optic atrophy, and eye abnormalities have been observed. Mental retardation, blindness, and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following in utero exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia, corneal leukoma, cleft palate, cleft lip, schizencephaly, and microcephaly.

Spontaneous abortion and stillbirth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. Low birth weight and growth retardation have also been reported.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

**Hemorrhagic tendencies or blood dyscrasias.**

**Recent or contemplated surgery of:** (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces.

**Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms-cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis.

**Threatened abortion,** eclampsia and preeclampsia.

**Inadequate laboratory facilities.**

**Unsupervised patients with senility,** alcoholism, or psychosis or other lack of patient cooperation.

**Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding.

**Miscellaneous:** major regional, lumbar block anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

(Back to top)

**1.1.1.6 WARNINGS**

The most serious risks associated with anticoagulant therapy with warfarin sodium are hemorrhage in any tissue or organ and, less frequently (<0.1%), necrosis and/or gangrene of skin and other tissues. The risk of hemorrhage is related to the level of
intensity and the duration of anticoagulant therapy. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolization in untreated cases.

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. COUMADIN (Warfarin Sodium), a narrow therapeutic range (index) drug, may be affected by factors such as other drugs and dietary Vitamin K. Dosage should be controlled by periodic determinations of PT/INR or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage PT. When heparin and COUMADIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Caution should be observed when COUMADIN is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage, necrosis, and/or gangrene is present.

Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, thereby increasing the risk of complications from systemic cholesterol microembolization, including the "purple toes syndrome." Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot, or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, hematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis, or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterized by a dark, purplish or mottled color of the toes, usually occurring between 3-10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple color of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes; waxing and waning of the color over time. While the purple toes syndrome is reported to be reversible, some cases progress to gangrene.

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or necrosis which may require debridement of the affected area, or may lead to amputation.

**Heparin-induced thrombocytopenia:** COUMADIN should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).

A severe elevation (>50 seconds) in activated partial thromboplastin time (aPTT) with a PT/INR in the desired range has been identified as an indication of increased risk of postoperative hemorrhage.

The decision to administer anticoagulants in the following conditions must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits:

**Lactation:** Based on very limited published data, warfarin has not been detected in the breast milk of mothers treated with warfarin. The same limited published data reports that some breast-fed infants, whose mothers were treated with warfarin, had prolonged prothrombin times, although not as prolonged as those of the mothers. The decision to breast-feed should be undertaken only after careful consideration of the available alternatives. Women who are breast-feeding and anticoagulated with warfarin should be very carefully monitored so that recommended PT/INR values are not exceeded. It is prudent to perform coagulation tests and to evaluate vitamin K status in infants at risk for bleeding tendencies before advising women taking warfarin to breast-feed. Effects in premature infants have not been evaluated.

**Severe to moderate hepatic or renal insufficiency.**

**Infectious diseases or disturbances of intestinal flora:** sprue, antibiotic therapy.

**Trauma** which may result in internal bleeding.

**Surgery or trauma** resulting in large exposed raw surfaces.

**Indwelling catheters.**

**Severe to moderate hypertension.**

**Known or suspected deficiency in protein C mediated anticoagulant response:** Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis, and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these
conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concomitant anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimize the incidence of tissue necrosis. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

**Miscellaneous:** polycythemia vera, vasculitis, and severe diabetes.

Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported.

In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to COUMADIN have been reported. Exaggerated therapeutic responses have been reported in other patients.

Patients with congestive heart failure may exhibit greater than expected PT/INR response to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

*(back to top)*

1.1.1.7 **PRECAUTIONS**

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medications, including botanicals, may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient’s response with additional PT/INR determinations in the period immediately after discharge from the hospital, and whenever other medications, including botanicals, are initiated, discontinued or taken irregularly. The following factors are listed for reference; however, other factors may also affect the anticoagulant response.

Drugs may interact with COUMADIN through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with COUMADIN are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and altered physiologic control loop for vitamin K metabolism (hereditary resistance). Pharmacokinetic mechanisms for drug interactions with COUMADIN are mainly enzyme induction, enzyme inhibition, and reduced plasma protein
It is important to note that some drugs may interact by more than one mechanism.

The following factors, alone or in combination, may be responsible for increased PT/INR response:

<table>
<thead>
<tr>
<th>ENDOGENOUS FACTORS:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>blood dyscrasias--</td>
<td>diarrhea</td>
</tr>
<tr>
<td></td>
<td>hyperthyroidism</td>
</tr>
<tr>
<td>see CONTRAINDICATIONS</td>
<td>elevated temperature</td>
</tr>
<tr>
<td></td>
<td>poor nutritional state</td>
</tr>
<tr>
<td>cancer</td>
<td>hepatic disorders</td>
</tr>
<tr>
<td></td>
<td>steatorrhea</td>
</tr>
<tr>
<td>collagen vascular disease</td>
<td>infectious hepatitis</td>
</tr>
<tr>
<td></td>
<td>vitamin K deficiency</td>
</tr>
<tr>
<td>congestive heart failure</td>
<td>jaundice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXOGENOUS FACTORS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential drug interactions with COUMADIN are listed below by drug class and by specific drugs.</td>
</tr>
</tbody>
</table>

### Classes of Drugs

<table>
<thead>
<tr>
<th>5-lipoxygenase Inhibitor</th>
<th>Antiparasitic/Antimicrobials</th>
<th>HMG-CoA Reductase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic Stimulants, Central</td>
<td>Antiplatelet Drugs/Effects</td>
<td>Inhibitors *<em>/</em></td>
</tr>
<tr>
<td>Alcohol Abuse Reduction</td>
<td>Antithyroid Drugs *<em>/</em></td>
<td>Leukotriene Receptor Antagonist</td>
</tr>
<tr>
<td>Preparations</td>
<td>Beta-Adrenergic Blockers</td>
<td>Monoamine Oxidase Inhibitors</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Cholelitholytic Agents</td>
<td>Narcotics, prolonged</td>
</tr>
<tr>
<td>Anesthetics, Inhalation</td>
<td>Diabetes Agents, Oral</td>
<td>Nonsteroidal Anti-Inflammatory</td>
</tr>
<tr>
<td>Antiandrogen</td>
<td>Diuretics *<em>/</em></td>
<td>Agents</td>
</tr>
<tr>
<td>Antiarrhythmics *<em>/</em></td>
<td>Fungal Medications, Intravaginal,</td>
<td>Proton Pump Inhibitors</td>
</tr>
<tr>
<td>Antibiotics *<em>/</em></td>
<td>Systemic *<em>/</em></td>
<td>Psychostimulants</td>
</tr>
<tr>
<td>Aminoglycosides (oral)</td>
<td>Gastric Acidity and Peptic</td>
<td>Pyrazolones</td>
</tr>
<tr>
<td>Cephalosporins, parenteral</td>
<td>Ulcer Agents *<em>/</em></td>
<td>Salicylates</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Gastrointestinal</td>
<td>Selective Serotonin</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Prokinetic Agents</td>
<td>Reuptake Inhibitors</td>
</tr>
<tr>
<td>Penicillins, intravenous,</td>
<td>Ulcerative Colitis Agents</td>
<td>Steroids, Adrenocortical *<em>/</em></td>
</tr>
<tr>
<td>high dose</td>
<td>Gout Treatment Agents</td>
<td>Steroids, Anabolic (17-Alkyl</td>
</tr>
<tr>
<td>Quinolones (fluoroquinolones)</td>
<td>Hemorrhheologic Agents</td>
<td>Testosterone Derivatives)</td>
</tr>
<tr>
<td>Sulfonamides, long acting</td>
<td>Hepatotoxic Drugs</td>
<td>Thrombolytics</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Hyperglycemic Agents</td>
<td>Thyroid Drugs</td>
</tr>
<tr>
<td>Anticoagulants *<em>/</em></td>
<td>Hypertensive Emergency Agents</td>
<td>Tuberculosis Agents *<em>/</em></td>
</tr>
<tr>
<td>Anticonvulsants *<em>/</em></td>
<td>Hypnotics *<em>/</em></td>
<td>Uricosuric Agents</td>
</tr>
<tr>
<td>Antidepressants *<em>/</em></td>
<td>Hypolipidemics *<em>/</em></td>
<td>Vaccines</td>
</tr>
<tr>
<td>Antimalarial Agents</td>
<td>Bile Acid-Binding Resins *<em>/</em></td>
<td>Vitamins *<em>/</em></td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Antineoplastics *<em>/</em></td>
<td>Fibric Acid Derivatives</td>
<td></td>
</tr>
</tbody>
</table>

### Specific Drugs Reported

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>Fluorouracil</th>
<th>Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol *<em>/</em></td>
<td>Flutamide</td>
<td>Penicillin G, intravenous</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Fluvastatin</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Aminosalicylic acid</td>
<td>Fluvoxamine</td>
<td>Phenytoin *<em>/</em></td>
</tr>
<tr>
<td>Amiodarone HCl</td>
<td>Heparin</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Geftinib</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Atorvastatin *<em>/</em></td>
<td>Gemfibrozil</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Glucagon</td>
<td>Pravastatin *<em>/</em></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Halothane</td>
<td>Prednisone *<em>/</em></td>
</tr>
<tr>
<td>Cefamandole</td>
<td>Heparin</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Ibuprofen</td>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Cefoperazine</td>
<td>Ilosafamide</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>Indomethacin</td>
<td>Propylthiouracil *<em>/</em></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Influenza virus vaccine</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Itraconazole</td>
<td>Quinine</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Ketoprofen</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>Ketorolac</td>
<td>Ranitidine *<em>/</em></td>
</tr>
<tr>
<td>Chenoiodiol</td>
<td>Lansoprazole</td>
<td>Rofecoxib</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Levamisole</td>
<td>Sertraline</td>
</tr>
<tr>
<td>Chloral hydrate *<em>/</em></td>
<td>Levofoxacin</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Chloropropamide</td>
<td>Levothyroxine</td>
<td>Stanozolol</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Levofloxacin</td>
<td>Streptokinase</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Lovastatin</td>
<td>Sulfamethizole</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Mefenamic acid</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Methimazole *<em>/</em></td>
<td>Sulfapyrazone</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Methyldopa</td>
<td>Sulfisoxazole</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Methylphenidate</td>
<td>Sulindac</td>
</tr>
<tr>
<td>Coumadin overdose</td>
<td>Methylsalicylate ointment</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Cyclophosphamide *<em>/</em></td>
<td>(topical)</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Danazol</td>
<td>Metronidazole</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Dextrans</td>
<td>Miconazole</td>
<td>Ticarcillin</td>
</tr>
<tr>
<td>Dextrothyroxine</td>
<td>(intravaginal, systemic)</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Moricizine hydrochloride *<em>/</em></td>
<td>Tissue plasminogen</td>
</tr>
</tbody>
</table>
**Diclofenac**  nalidixic acid  activator (t-PA)
**Dicumarol**  naproxen  tolbutamide
**Diflunisal**  neomycin  tramadol
**Disulfiram**  norfloxacin  trimethoprim/sulfamethoxazole
**Doxycycline**  ofloxacin  urokinase
**Erythromycin**  olsalazine  valproate
**Esomeprazole**  omeprazole  vitamin E
**Etacrynic Acid**  oxandrolone  zafirlukast
**Fenofibrate**  oxaprozin  zileuton
**Fenoprofen**  oxymetholone
**Fluconazole**  pantoprazole

also: other medications affecting blood elements which may modify hemostasis
dietary deficiencies
prolonged hot weather
unreliable PT/INR determinations

**/* Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for
DECREASED PT/INR response:

<table>
<thead>
<tr>
<th><strong>ENDOGENOUS FACTORS:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>edema</td>
</tr>
<tr>
<td>hypothyroidism</td>
</tr>
<tr>
<td>hereditary coumarin</td>
</tr>
<tr>
<td>resistance</td>
</tr>
<tr>
<td>nephrotic syndrome</td>
</tr>
<tr>
<td>hyperlipemia</td>
</tr>
</tbody>
</table>

EXOGENOUS FACTORS:

Potential drug interactions with COUMADIN are listed below by drug class and by specific drugs.

<table>
<thead>
<tr>
<th>Classes of Drugs</th>
<th>Antithyroid Drugs *<em>/</em></th>
<th>HMG-CoA Reductase Inhibitors *<em>/</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Cortic Steroid Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Barbiturates</td>
<td>Imunosuppressives</td>
</tr>
<tr>
<td>Antianxiety Agents</td>
<td>Diuretics *<em>/</em></td>
<td>Oral Contraceptives,</td>
</tr>
<tr>
<td>Antiarrhythmics **/*</td>
<td>Enteral Nutritional Supplements</td>
<td></td>
</tr>
<tr>
<td>Antibiotics *<em>/</em></td>
<td>Fungal Medications, Systemic *<em>/</em></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants **/*</td>
<td>Gastric Acidity and</td>
<td>Modulators</td>
</tr>
</tbody>
</table>

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**Specific Drugs Reported**

<table>
<thead>
<tr>
<th>Antidepressants *<em>/</em></th>
<th>Peptic Ulcer Agents *<em>/</em></th>
<th>Steroids, Adrenocortical *<em>/</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithistamines</td>
<td>Hypnotics *<em>/</em></td>
<td>Tuberculosis Agents *<em>/</em></td>
</tr>
<tr>
<td>Antineoplastics *<em>/</em></td>
<td>Hypolipidemics *<em>/</em></td>
<td>Vitamins *<em>/</em></td>
</tr>
<tr>
<td>Antipsychotic Medications</td>
<td>Bile Acid-Binding Resins *<em>/</em></td>
<td></td>
</tr>
<tr>
<td>alcohol *<em>/</em></td>
<td>COUMADIN underdosage</td>
<td>phenytoin *<em>/</em></td>
</tr>
<tr>
<td>aminogluthethimide</td>
<td>cyclophosphamide *<em>/</em></td>
<td>pravastatin *<em>/</em></td>
</tr>
<tr>
<td>amobarbital</td>
<td>dicloxacillin</td>
<td>prednisone *<em>/</em></td>
</tr>
<tr>
<td>atorvastatin *<em>/</em></td>
<td>ethchlorvynol</td>
<td>primidone</td>
</tr>
<tr>
<td>azathioprine</td>
<td>glucorticamide *<em>/</em></td>
<td>propylthiouracil *<em>/</em></td>
</tr>
<tr>
<td>butabarbital</td>
<td>griseofulvin</td>
<td>raloxifene</td>
</tr>
<tr>
<td>butalbital</td>
<td>haloperidol</td>
<td>ranitidine *<em>/</em></td>
</tr>
<tr>
<td>carbamazepine</td>
<td>meprobamate</td>
<td>rifampin</td>
</tr>
<tr>
<td>chloral hydrate *<em>/</em></td>
<td>6-mercaptopurine</td>
<td>secobarbital</td>
</tr>
<tr>
<td>chlordiazepoxide</td>
<td>methimazole *<em>/</em></td>
<td>spironolactone</td>
</tr>
<tr>
<td>chlorothalidone</td>
<td>moricizine hydrochloride *<em>/</em></td>
<td>sucralfate</td>
</tr>
<tr>
<td>cholestyramine *<em>/</em></td>
<td>nafcillin</td>
<td>trazodone</td>
</tr>
<tr>
<td>clozapine</td>
<td>paraldehyde</td>
<td>vitamin C (high dose)</td>
</tr>
<tr>
<td>corticocotropin</td>
<td>pentobarbital</td>
<td>vitamin K</td>
</tr>
<tr>
<td>cortisone</td>
<td>phenobarbital</td>
<td></td>
</tr>
<tr>
<td>also: diet high in vitamin K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unreliable PT/INR determinations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**/* Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of COUMADIN on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

**Botanical (Herbal) Medicines:** Caution should be exercised when botanical medicines (botanicals) are taken concomitantly with COUMADIN. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and COUMADIN. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the
patient’s response with additional PT/INR determinations when initiating or discontinuing botanicals.

Specific botanicals reported to affect COUMADIN therapy include the following:

- Bromelains, danshen, dong quai (*Angelica sinensis*), garlic, Ginkgo biloba, ginseng, and cranberry products are associated most often with an INCREASE in the effects of COUMADIN.

- Coenzyme Q\textsubscript{10} (ubidecarenone) and St. John’s wort are associated most often with a DECREASE in the effects of COUMADIN.

Some botanicals may cause bleeding events when taken alone (e.g., garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of COUMADIN. Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of COUMADIN.

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed.

<table>
<thead>
<tr>
<th>Botanicals that contain coumarins with potential anticoagulant effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa</td>
</tr>
<tr>
<td>Angelica (Dong Quai)</td>
</tr>
<tr>
<td>Aniseed</td>
</tr>
<tr>
<td>Arnica</td>
</tr>
<tr>
<td>Asa Foetida</td>
</tr>
<tr>
<td>Bogbean (^1)</td>
</tr>
<tr>
<td>Boldo</td>
</tr>
<tr>
<td>Buchu</td>
</tr>
<tr>
<td>Capsicum (^2)</td>
</tr>
<tr>
<td>Cassia (^3)</td>
</tr>
<tr>
<td>Misc. botanicals with anticoagulant properties:</td>
</tr>
<tr>
<td>Bladder Wrack (<em>Fucus</em>)</td>
</tr>
<tr>
<td>Botanicals that contain salicylate and/or have antiplatelet properties:</td>
</tr>
<tr>
<td>Agrimony (^4)</td>
</tr>
<tr>
<td>Aloe Gel</td>
</tr>
<tr>
<td>Aspen</td>
</tr>
<tr>
<td>Black Cohosh</td>
</tr>
<tr>
<td>Black Haw</td>
</tr>
</tbody>
</table>

---

Approved v8.0 930018272 6.0
Botanicals with fibrinolytic properties:

<table>
<thead>
<tr>
<th>Bogbean</th>
<th>Ginkgo Biloba</th>
<th>Tamarind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassia 3</td>
<td>Ginseng (Panax) 5</td>
<td>Willow</td>
</tr>
<tr>
<td>Clove</td>
<td>Licorice 3</td>
<td>Wintergreen</td>
</tr>
</tbody>
</table>

Botanicals with coagulant properties:

<table>
<thead>
<tr>
<th>Agrimony 4</th>
<th>Mistletoe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenseal</td>
<td>Yarrow</td>
</tr>
</tbody>
</table>

1 Contains coumarins and salicylate.
2 Contains coumarins and has fibrinolytic properties.
3 Contains coumarins and has antiplatelet properties.
4 Contains salicylate and has coagulant properties.
5 Has antiplatelet and fibrinolytic properties.

**Effect on Other Drugs:** Coumarins may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

**Special Risk Patients:** COUMADIN (Warfarin Sodium) is a narrow therapeutic range (index) drug, and caution should be observed when warfarin sodium is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of hemorrhage is present.

Intramuscular (I.M.) injections of concomitant medications should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when COUMADIN (or warfarin) is administered concomitantly with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

Acquired or inherited warfarin resistance should be suspected if large daily doses of COUMADIN are required to maintain a patient's PT/INR within a normal therapeutic range.

**Information for Patients:** The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in
part dependent upon cooperative and well-instructed patients who communicate effectively with their physician. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g., aspirin and topical analgesics), other over-the-counter medications, and botanical (herbal) products (e.g., bromelains, coenzyme Q, danshen, dong quai, garlic, Ginkgo biloba, ginseng, and St. John’s wort) except on advice of the physician. Avoid alcohol consumption. Do not take COUMADIN during pregnancy and do not become pregnant while taking it (see CONTRAINDICATIONS). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to physician or clinic are needed to monitor therapy. Carry identification stating that COUMADIN is being taken. If the prescribed dose of COUMADIN is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of COUMADIN the next day to make up for missed doses. The amount of vitamin K in food may affect therapy with COUMADIN. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. You should also avoid intake of cranberry juice or any other cranberry products. Notify your health care provider if any of these products are part of your normal diet. Contact physician to report any illness, such as diarrhea, infection or fever. Notify physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness, or weakness. If therapy with COUMADIN is discontinued, patients should be cautioned that the anticoagulant effects of COUMADIN may persist for about 2 to 5 days. Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and mutagenicity studies have not been performed with COUMADIN. The reproductive effects of COUMADIN have not been evaluated.

Use in Pregnancy: Pregnancy Category X—See CONTRAINDICATIONS.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established, in randomized, controlled clinical trials. However, the use of COUMADIN in pediatric patients is well-documented for the prevention and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the pediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible changing warfarin requirements.

Geriatric Use: Patients 60 years or older appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin (see CLINICAL PHARMACOLOGY). COUMADIN is contraindicated in any unsupervised patient with senility. Caution should be observed with administration of warfarin sodium to elderly patients in any situation or physical condition where added risk of hemorrhage is
present. Lower initiation and maintenance doses of COUMADIN are recommended for elderly patients (see Dosage and Administration).

1.1.1.8 ADVERSE REACTIONS

Potential adverse reactions to COUMADIN may include:

- Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR. (See Overdosage: Treatment.)

- Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g., tumor, ulcer, etc.

- Necrosis of skin and other tissues. (See WARNINGS.)

- Adverse reactions reported infrequently include: hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritus, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

Rare events of tracheal or tracheobronchial calcification have been reported in association with long-term warfarin therapy. The clinical significance of this event is unknown.

Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

1.1.1.9 OVERDOSAGE

Signs and Symptoms: Suspected or overt abnormal bleeding (e.g., appearance of blood in stools or urine, hematuria, excessive menstrual bleeding, melena,
petechiae, excessive bruising or persistent oozing from superficial injuries) are early manifestations of anticoagulation beyond a safe and satisfactory level.

**Treatment:** Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing COUMADIN therapy and if necessary, by administration of oral or parenteral vitamin K₁. (Please see recommendations accompanying vitamin K₁ preparations prior to use.)

Such use of vitamin K₁ reduces response to subsequent COUMADIN (Warfarin Sodium) therapy. Patients may return to a pretreatment thrombotic status following the rapid reversal of a prolonged PT/INR. Resumption of COUMADIN administration reverses the effect of vitamin K₁ and a therapeutic PT/INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

If minor bleeding progresses to major bleeding, give 5 to 25 mg (rarely up to 50 mg) parenteral vitamin K₁. In emergency situations of severe hemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of fresh whole blood or fresh frozen plasma, or by giving commercial Factor IX complex.

A risk of hepatitis and other viral diseases is associated with the use of these blood products; Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to COUMADIN (Warfarin Sodium) overdosage.

Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X which are also depressed along with the levels of Factor IX as a result of COUMADIN treatment. Packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary edema in elderly patients or patients with heart disease.

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**1.1.1.10 DOSAGE AND ADMINISTRATION**

The dosage and administration of COUMADIN must be individualized for each patient according to the particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR. (See **LABORATORY CONTROL** below for full discussion on INR.)

**Venous Thromboembolism (including pulmonary embolism):** Available clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism and minimizes the risk of hemorrhage associated with higher INRs. In patients with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman et al, 1995 and Schulman et al, 1997).
Atrial Fibrillation: Five recent clinical trials evaluated the effects of warfarin in patients with non-valvular atrial fibrillation (AF). Meta-analysis findings of these studies revealed that the effects of warfarin in reducing thromboembolic events including stroke were similar at either moderately high INR (2.0-4.5) or low INR (1.4-3.0). There was a significant reduction in minor bleeds at the low INR. Similar data from clinical studies in valvular atrial fibrillation patients are not available. The trials in non-valvular atrial fibrillation support the American College of Chest Physicians’ (ACCP) recommendation that an INR of 2.0-3.0 be used for long term warfarin therapy in appropriate AF patients.

Post-Myocardial Infarction: In post-myocardial infarction patients, COUMADIN therapy should be initiated early (2-4 weeks post-infarction) and dosage should be adjusted to maintain an INR of 2.5-3.5 long-term. The recommendation is based on the results of the WARIS study in which treatment was initiated 2 to 4 weeks after the infarction. In patients thought to be at an increased risk of bleeding complications or on aspirin therapy, maintenance of COUMADIN therapy at the lower end of this INR range is recommended.

Mechanical and Bioprosthetic Heart Valves: In patients with mechanical heart valve(s), long term prophylaxis with warfarin to an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valve(s), based on limited data, the American College of Chest Physicians recommends warfarin therapy to an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or prior thromboembolism, consideration should be given for longer term therapy.

Recurrent Systemic Embolism: In cases where the risk of thromboembolism is great, such as in patients with recurrent systemic embolism, a higher INR may be required.

An INR of greater than 4.0 appears to provide no additional therapeutic benefit in most patients and is associated with a higher risk of bleeding.

Initial Dosage: The dosing of COUMADIN must be individualized according to patient's sensitivity to the drug as indicated by the PT/INR. Use of a large loading dose may increase the incidence of hemorrhagic and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Lower initiation and maintenance doses are recommended for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR response to COUMADIN (see PRECAUTIONS). Based on limited data, Asian patients may also require lower initiation and maintenance doses of COUMADIN (see CLINICAL PHARMACOLOGY). It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5 mg per day with dosage adjustments based on the results of PT/INR determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.
Duration of Therapy: The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Missed Dose: The anticoagulant effect of COUMADIN persists beyond 24 hours. If the patient forgets to take the prescribed dose of COUMADIN at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

Intravenous Route of Administration: COUMADIN for Injection provides an alternate administration route for patients who cannot receive oral drugs. The IV dosages would be the same as those that would be used orally if the patient could take the drug by the oral route. COUMADIN for Injection should be administered as a slow bolus injection over 1 to 2 minutes into a peripheral vein. It is not recommended for intramuscular administration. The vial should be reconstituted with 2.7 mL of sterile Water for Injection and inspected for particulate matter and discoloration immediately prior to use. Do not use if either particulate matter and/or discoloration is noted. After reconstitution, COUMADIN for Injection is chemically and physically stable for 4 hours at room temperature. It does not contain any antimicrobial preservative and, thus, care must be taken to assure the sterility of the prepared solution. The vial is not recommended for multiple use and unused solution should be discarded.

LABORATORY CONTROL The PT reflects the depression of vitamin K dependent Factors VII, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific method used in his laboratory. The degree of anticoagulation indicated by any range of PTs may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT/INR results stabilize in the therapeutic range. Intervals between subsequent PT/INR determinations should be based upon the physician's judgment of the patient's reliability and response to COUMADIN in order to maintain the individual within the therapeutic range. Acceptable intervals for PT/INR determinations are normally within the range of one to four weeks after a stable dosage has been determined. To ensure adequate control, it is recommended that additional PT tests are done when other warfarin products are interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (see PRECAUTIONS).

Different thromboplastin reagents vary substantially in their sensitivity to sodium warfarin-induced effects on PT. To define the appropriate therapeutic regimen it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP), a sensitive thromboplastin reagent prepared from human brain.

A system of standardizing the PT in oral anticoagulant control was introduced by the World Health Organization in 1983. It is based upon the determination of an International Normalized Ratio (INR) which provides a common basis for
communication of PT results and interpretations of therapeutic ranges. The INR system of reporting is based on a logarithmic relationship between the PT ratios of the test and reference preparation. The INR is the PT ratio that would be obtained if the International Reference Preparation (IRP), which has an ISI of 1.0, was used to perform the test. Early clinical studies of oral anticoagulants, which formed the basis for recommended therapeutic ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: \( \text{INR} = (\text{observed PT ratio})^{\text{ISI}} \) where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio. 

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.

| TABLE 3: Relationship Between INR and PT Ratios For Thromboplastins With Different ISI Values (Sensitivities) |
|---------------------------------------------------|-------|-------|-------|-------|-------|-------|
| PT RATIOS                                         | ISI 1.0 | ISI 1.4 | ISI 1.8 | ISI 2.3 | ISI 2.8 |
| INR=2.0-3.0                                       | 2.0-3.0 | 1.6-2.2 | 1.5-1.8 | 1.4-1.6 | 1.3-1.5 |
| INR=2.5-3.5                                       | 2.5-3.5 | 1.9-2.4 | 1.7-2.0 | 1.5-1.7 | 1.4-1.6 |

**TREATMENT DURING DENTISTRY AND SURGERY**  The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of COUMADIN (Warfarin Sodium) to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of COUMADIN therapy. When discontinuing COUMADIN even for a short period of time, the benefits and risks should be strongly considered.
CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of COUMADIN is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that COUMADIN therapy be overlapped with heparin for 4 to 5 days, until COUMADIN has produced the desired therapeutic response as determined by PT/INR. When COUMADIN has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

COUMADIN may increase the aPTT test, even in the absence of heparin. During initial therapy with COUMADIN, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and COUMADIN should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

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1.1.1.11 HOW SUPPLIED

Tablets: For oral use, single scored with one face imprinted numerically with 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 or 10 superimposed and inscribed with "COUMADIN" and with the opposite face plain. COUMADIN is available in bottles and Hospital Unit-Dose Blister Packages with potencies and colors as follows:

<table>
<thead>
<tr>
<th>Potency</th>
<th>100's NDC</th>
<th>1000's NDC</th>
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<tr>
<td>1 mg pink</td>
<td>0056-0169-70</td>
<td>0056-0169-90</td>
<td>0056-0169-75</td>
</tr>
<tr>
<td>2 mg lavender</td>
<td>0056-0170-70</td>
<td>0056-0170-90</td>
<td>0056-0170-75</td>
</tr>
<tr>
<td>2-1/2 mg green</td>
<td>0056-0176-70</td>
<td>0056-0176-90</td>
<td>0056-0176-75</td>
</tr>
<tr>
<td>3 mg tan</td>
<td>0056-0188-70</td>
<td>0056-0188-90</td>
<td>0056-0188-75</td>
</tr>
<tr>
<td>4 mg blue</td>
<td>0056-0168-70</td>
<td>0056-0168-90</td>
<td></td>
</tr>
<tr>
<td>5 mg peach</td>
<td>0056-0172-70</td>
<td>0056-0172-90</td>
<td>0056-0172-75</td>
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<tr>
<td>6 mg teal</td>
<td>0056-0189-70</td>
<td>0056-0189-90</td>
<td>0056-0189-75</td>
</tr>
<tr>
<td>7-1/2 mg yellow</td>
<td>0056-0173-70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg white (Dye Free)</td>
<td>0056-0174-70</td>
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Protect from light. Store at controlled room temperature (59°-86°F, 15°-30°C). Dispense in a tight, light-resistant container as defined in the USP.
Hospital Unit-Dose Blister Packages are to be stored in carton until contents have been used.

**Injection:** Available for intravenous use only. Not recommended for intramuscular administration. Reconstitute with 2.7 mL of sterile Water for Injection to yield 2 mg/mL. Net contents 5.4 mg lyophilized powder. Maximum yield 2.5 mL.

5 mg vial (box of 6) NDC 0590-0324-35


After reconstitution, store at controlled room temperature (59°-86°F, 15°-30°C) and use within 4 hours. Do not refrigerate. Discard any unused solution.

1.1.1.12 **REFERENCES**


Distributed by:

Bristol-Myers Squibb Company

Princeton, NJ 08543 U.S.A.

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11.1.13 PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual or relative size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.
STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

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 Subjects with Nonvalvular Atrial Fibrillation

(The ARISTOTLE study)

PROTOCOL CV185030

V2
## DOCUMENT HISTORY

<table>
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<tr>
<th>Version Number</th>
<th>Date</th>
<th>Description of Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>01-Aug-2007</td>
<td>Original Version</td>
</tr>
</tbody>
</table>
| 2.0            | 11-May-2010| This version of the SAP includes mainly changes to the SAP to align with the protocol amendments to date, the DMC charter and to address FDA’s questions. Other changes include re-organization of information into different sections to follow most up to date BMS SAP template and changes to follow the BMS and apixaban-specific Analysis and Reporting standards. Section 1 - Background and Rationale Removed information (outdated) regarding other apixaban studies. Section 1.2 - Schedule of Analysis Refers to Section 7.6.3 (Interim Analysis) rather than the SAP for the interim analysis Section 2.1 - Study Design Updated language to align with the text in Protocol Amendment 7 Section 2.3.1 - Blinding Corrected the name of the Department at BMS with access to the randomization codes Section 2.4 - Protocol Amendments Updated information regarding protocol amendments Section 3.2 - Secondary Objectives Updated the description of secondary objectives as per Protocol Amendment 10 4.1.2 - Secondary Efficacy Outcomes Added the secondary efficacy endpoint (composite of stroke, systemic embolism or major bleeding in warfarin naive subjects) corresponding to one of the secondary objectives of the study Section 5 - Sample Size and Power Included the justification for the sample size increase which was the basis for Protocol Amendment 7
### Section 6 - Study Periods, Treatment Regimens and Populations for Analyses

This section replaces Section 6 on Cohorts and Data Sets in SAP V1 to follow the most recent version of the BMS SAP template. Clarified the definition of Treatment Period for the analyses of each safety endpoint.

The information previously contained in Section 6 of SAP V1 was re-organized into the subsections of the revised Section 6 and the statement regarding cohorts and specific populations used for each analysis was moved to Section 7.

Noted that the efficacy cut-off date will be decided upon and documented prior to database unblinding.

### Section 7.1 - General Methods

Added the testing strategy that will be used for the analyses to address FDA’s comments.

Added the rule for combining investigative sites in the analyses as required by ICH E9. When using a Cox proportional hazards model stratified by prior warfarin/VKA status and investigative site, site will be pooled to the Geographic Region level.

### Section 7.3.2 - Demographic and Baseline Characteristics

Added BMI, weight, level of renal impairment, CHADS2 score and individual subgroups based on components of CHADS2 score as baseline subgroups of clinical relevance that will be summarized. Added Appendix 2 with a list of countries randomizing subjects in the study and the associated regions.

### Sections 7.4.1 and 7.4.3 - Study Therapy and Concomitant Medications

Clarified that exposure to study drug and concomitant medication summaries will be based on the treated subjects population.

Corrected the formula to calculate treatment compliance.

### Section 7.4.2 - INR Control

Clarified that INR summaries will be based on the randomized subjects population.

Corrected the low and high cutoffs from 0.9 and 15 to 0.8 and 12 to capture the lower and upper limits of quantification, respectively.
<p>| Changed the method to summarize the INR from a stepwise approach which assumed that an INR value remains constant between visits (which could provide an anti-conservative summary for INR control) to a more clinically meaningful and referenced method (Rosendaal) |
| Removed information regarding how values &lt;LLQ or &gt;ULQ will be summarized given that the summary cutoffs are now aligned with LLQ and ULQ as described above |
| Section 7.5 and Subsections (Efficacy) and Section 7.6 and Subsections (Safety) |
| The main changes made in these sections are to address FDA’s comments |
| Included (Section 7.5) supportive censoring schema for sensitivity analyses (On Treatment analyses) associated with the NI test. As previously requested by the FDA, the SAP included, as a sensitivity analysis, an on-treatment analysis which censors subjects who do not experience a primary event up until 30 days after the last dose of study drug. Another sensitivity analysis is now added using a censoring scheme for subjects who do not experience a primary event up until 2 days after the last dose of study drug |
| Deleted from Section 7.5.2 the formal superiority test and associated sensitivity analyses for the combined endpoint of stroke, systemic embolism and major bleeding (net-benefit). |
| Added formal tests of superiority for major bleeding (Section 7.6.1) and for all-cause death (Section 7.5.2) in alignment with the objectives of the study as documented in Amendment 10. |
| Other changes are described below. |
| Clarified that the supportive censoring scheme will be used for sensitivity analyses associated with the NI test. |
| Changed the time periods that will be used to test the proportional hazards assumption from 0-6, 6-12, 12-18, +18 to 0-&lt;9, 9-&lt;18, 18-&lt;27, 27+ to make the test more meaningful given the increase in the estimated average follow-up documented in Section 5. The description of the visual check of the proportional hazards assumption has been aligned with the proportional hazards model used (i.e. a model which includes prior warfarin/VKA status and geographic region as stratification factors as described in the Section 7.1 modification). |</p>
<table>
<thead>
<tr>
<th>Section 7.6 - Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moved information previously in Section 6 of the SAP V1 regarding analyses populations for efficacy endpoints to the corresponding subsections of Section 7.</td>
</tr>
<tr>
<td>Added race, ethnicity, weight, level of renal impairment and CHADS2 scores and individual subgroups based on components of CHADS2 score at baseline as subgroups of clinical relevance for the subgroup analyses of the primary efficacy endpoint.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 7.6 - Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moved information previously in Section 6 of the SAP V1 regarding analyses populations for safety endpoints to Section 7.6.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 7.6.2.2 - Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed reference to the no longer applicable GD SOP 12 to CT SOP 109. The previous exception no longer applies and is documented in the definition of Treatment Period in Section 6 of this SAP.</td>
</tr>
<tr>
<td>Added summaries for SAEs, most common SAEs, AEs related to elevations in LFTs and neurologic AEs.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Section 7.6.2.3 - Laboratory Data</th>
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</thead>
<tbody>
<tr>
<td>Specified the analysis period for each analysis. For shift analysis corrected that low values correspond to &lt; LLN (lower limit of normal) rather than &lt; ULN (upper limit of normal) as incorrectly written in SAP V1.</td>
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<tr>
<th>Section 7.6.3 - Interim Analysis</th>
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<tr>
<td>Aligns the interim stopping rule with the stopping rule that had been developed with input by the DMC early in the study (and prior to the DMC having reviewed any data). The other changes in this section were made to address an FDA’s comment to document the effect of the interim analysis to assess superiority on the final NI assessment for the primary efficacy endpoint and the final superiority tests.</td>
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<tr>
<th>Section 8 (and subsections) - Conventions</th>
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<tr>
<td>Changes made to these sections are mainly to align the definitions with the BMS and apixaban Analysis and Reporting standards.</td>
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<tr>
<td>Specified the imputation rules for missing or partial dates for analysis of efficacy endpoints and bleeding endpoints.</td>
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<td>Expanded the definition of baseline measurements (for labs or vital signs) to account for cases when more than one value could qualify as baseline.</td>
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</table>
| | Align the day ranges for analyses based on visit windows with the BMS standards. Day ranges in Table 8.3 are expanded to include up to Month 59 nominal visit following changes implemented in Administrative Letter #5. The algorithm to derive the day ranges for the additional visits is the same as that used to derive the day ranges for the previous visits.

| | Expanded the criteria to select which measurement (for labs or vital signs) to include in the analysis when multiple measurements are available at a single visit.

| | Section 10 - Simulation Studies

| | This section was added to address an FDA’s comment. Document the bias-adjustment made to the RR point estimate if the study is terminated at the interim analysis.
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1 BACKGROUND AND RATIONALE

Apixaban is a novel, selective, orally active inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) as an anticoagulant and antithrombotic agent.

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), thereby 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. In the OASIS-5 trial of acute coronary syndromes, fondaparinux (at a dose of 2.5 mg subcutaneous per day) was shown to be equally effective in preventing thrombotic events as enoxaparin, but with half the bleeding risk. These findings highlight the potential of FXa inhibition to be an effective and safe approach towards anticoagulation. Given the established utility of FXa inhibition in prevention and treatment of venous and arterial thrombotic disease, an orally available agent would be desirable.

Thrombotic disorders are a major cause of mortality and morbidity. Previous work has shown that effective antithrombotic therapy may treat or prevent acute coronary syndrome (ACS), venous thromboembolism (VTE) and stroke, but all of the presently available agents have liabilities.

In the past 20 years, there have been significant advances in our understanding of atrial fibrillation (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 coumarins or 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). Despite their 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. Failure to maintain 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. 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.\(^3,4\) 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.\(^5\)

These factors indicate that large numbers of subjects with AF and additional risk factors for stroke are either not being offered treatment with warfarin, are intolerant of 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 conversely, 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. BMS is developing apixaban as an antithrombotic for subjects with AF who are at risk for stroke with the above properties in mind.

To establish the safety and efficacy of apixaban in the prevention of stroke and systemic embolism in subjects with AF and stroke risk factor(s), BMS is undertaking the present study (CV185030), a Phase 3 parallel arm study using warfarin as an active comparator. Since warfarin has been shown to be highly effective in preventing stroke in this population, a placebo controlled trial would not be ethical. The study is randomized and conducted in a double blinded fashion to minimize the risk of bias.
1.1 Research Hypothesis

Apixaban is noninferior to warfarin for prevention of stroke (ischemic or hemorrhagic) or systemic embolism in subjects with AF and additional risk factor(s) for stroke.

1.2 Schedule of Analyses

The expected duration of the study, from first subject first visit through last subject, last visit is approximately 40 months. There are three study periods:

- a screening period of up to 14 days,
- a treatment period lasting until the earlier of a subject’s discontinuation of study drug or the attainment of approximately 448 primary efficacy events, and
- a follow-up period lasting until the latter of at least 30 days after discontinuation of study drug or the attainment of approximately 448 primary efficacy events.

The final analyses will be performed once approximately 448 primary efficacy events are confirmed by the CEC and all subjects have been followed-up for at least 30 days after treatment discontinuation or are lost to follow-up. Throughout this document, “events confirmed by the CEC” refers to events that the investigator identified and were later confirmed by adjudication as well as events that, although not identified by the investigator as efficacy events (stroke, systemic embolism, or myocardial infarction), were later adjudicated as efficacy events by the CEC.

A formal interim analysis will be performed once approximately 50% (224) of the primary efficacy endpoint events have been confirmed by the CEC. The objective of this interim analysis is to determine whether apixaban is superior to warfarin for the primary efficacy endpoint. Further details can be found in Section 7.6.3.

2 STUDY DESCRIPTION

2.1 Study Design

Subjects with documented atrial fibrillation or flutter and at least one additional risk factor for stroke are potentially eligible for this trial. Subjects who meet inclusion criteria
and have none of the exclusion criteria will be asked to provide written informed consent and will be randomized into the study.

This study is designed to evaluate the efficacy and safety of apixaban compared to warfarin (INR target range 2.0-3.0) in subjects with nonvalvular AF with additional risk factor(s) for stroke. The primary endpoint, a composite of ischemic stroke, hemorrhagic stroke 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 40 months, but the final duration per subject will be determined by the time required to accrue 448 primary efficacy events. All subjects will be followed from randomization until the earliest of death, withdrawal of consent to be followed-up, loss to follow-up or the study end date. All attempts will be made to minimize the number of subjects that are lost to follow-up.

Eligible subjects will be randomized in a 1:1 ratio to either apixaban or warfarin. Each arm will contain ~9,000 subjects. 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. The two sets of tablets each subject receives will be distinguishable by color and size, but active apixaban tablets will match placebo apixaban tablets and active warfarin tablets will match placebo warfarin tablets to avoid unblinding of investigators and staff.

INR testing frequency will occur at least every month during the treatment period, more frequently during titration and if clinically indicated (see Section 2.2). 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 an INR value (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 for warfarin will rest with the Investigator.
All subjects will be followed for the development of stroke (ischemic or hemorrhagic), systemic embolism, myocardial infarction, death, bleeding, hospitalization or treatment discontinuation until the end of the study. Subjects will be followed-up until the latter of 30 days after treatment discontinuation or the attainment of 448 primary efficacy events. Follow-up of subjects who discontinued study drug will occur quarterly by a phone call. Approximately 30 days after the attainment of 448 primary efficacy events a telephone contact call will be made to all subjects (either on treatment or being followed up after treatment discontinuation). Serious adverse events (SAEs) and study outcomes will be documented at all follow-up contacts.

### 2.2 Treatment Group Assignment

At the time of enrollment, each subject will be assigned a unique sequential subject number by the IVRS. The subject number will consist of a unique digit number which is assigned sequentially within the study 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 criteria and does not meet any of the 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). Assignment will be in a 1:1 ratio by the IVRS. Randomization schedules will be generated and kept by the Randomization Center at BMS. At the time of randomization, the IVRS will assign each subject two container numbers, one for warfarin (active or placebo) and another for apixaban (placebo or active). Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the bottles containing study drug. Container numbers will be recorded on the Case Report Form (CRF).

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 ≤ 30 consecutive days of treatment with warfarin or another VKA in the past. Otherwise the subject will be classified as warfarin experienced.

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 blinded study drugs until the INR is < 2.0. Subjects will receive either active-apixaban
and warfarin-placebo, or apixaban-placebo and active-warfarin following randomization during a titration phase using a recommended daily dosing algorithm consisting of two initial daily doses of up to 6 mg of warfarin (or warfarin-placebo) 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, the final decision as to dose will rest with the Investigator. INR monitoring will begin on the 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.

For certain subjects who may be deemed to be at higher risk of bleeding with study drug, the lower dose of apixaban (2.5 mg BID) will be used. Subjects who fulfill any two of the following criteria will be assigned a 2.5mg BID apixaban (active or placebo) dose at the time of randomization only:

- Age ≥ 80 years
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL.

### 2.3 Blinding and Unblinding

#### 2.3.1 Blinding

This study will be conducted in double-blind fashion. To maintain the blind, study drug will be packaged using a double-dummy design in which the appropriate combinations of active tablets and placebo tablets matching the active treatments are provided. Subjects, Investigators, members of any of the administrative and adjudicating committees [with the possible exception of members of the Data Monitoring Committee (DMC) if needed], and the Sponsor’s staff conducting the study will not have access to individual subject treatment assignments. A designated member of the Randomization Center within the Drug Supply Management Department of BMS will have access to such assignments.
2.3.2 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. 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 subjects 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.

Every subject will be provided with an alert card. The alert card:

- Will indicate that the subject is participating in a double-blind clinical trial
- Provides the sponsor’s name (Bristol-Myers Squibb) and trial number (CV185030)
- Will note that the subject may be receiving either warfarin or an investigational anticoagulant drug (a factor Xa inhibitor)
- Includes contact numbers for the subject’s investigator to provide information to emergency medical personnel

The need to break the blind should first be discussed with the responsible Medical Monitor. A trial Help Line may also be used for this purpose.

2.4 Protocol Amendments

The protocol currently has 10 amendments. The table below summarizes the main purpose of each amendment (see amendment for further details).
<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Amendment Date</th>
<th>Main Purpose of Amendment</th>
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<tr>
<td>01</td>
<td>21-Nov-2006</td>
<td>To permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research studies. BMS will use DNA obtained from the blood sample and health information collected from the main clinical trial, CV185030 CRF, to study the association between genetic variation and drug response. BMS may also use the DNA to study the causes and further progression of acute coronary syndrome and other heart diseases. Samples from this and other clinical studies may also be used in conjunction to accomplish this objective.</td>
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<td>02</td>
<td>30-Jul-2007</td>
<td>First, to define the goal and method of achieving enrollment of warfarin naïve subjects. Second, to make changes to both the inclusion and exclusion criteria to aid in enrollment while preserving safety. Third, to refine the dosing procedure for starting study drugs to take into account subjects who are on non-warfarin vitamin K antagonists. Fourth, in response to investigators, national coordinators and ethics committees, to provide more detailed language regarding the management of subjects at the times of elective and emergent surgery and invasive procedures, as well as in the event of bleeding; and to provide similar guidance at the time of cardioversion. The amendment also clarifies the number and types of restricted treatments, as well as the approach to discontinuation and follow-up to help minimize subjects who might be lost to therapy or to follow-up. The amendment provides an updated definition of the prospectively defined safety “events of special interest” that are of concern to health authorities.</td>
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<td>03</td>
<td>24-Sep-2007</td>
<td>Site (France) specific - This amendment was written to answer specific requirements posed by the French Health Authority (AFSSAPS) with regards to: initial dosing of warfarin in elderly patients; providing guidance to investigators concerning measures to be taken in the event of hemorrhagic, thromboembolic and ischemic episodes or in the case of emergency surgery; addressing the possibility of reversing the study drug product; recommending the pyrazole NSAIDs (e.g. celecoxib) be considered prohibited agents; providing a card to all subjects in the study indicating their participation, types of treatments and the contact information of the appropriate investigator.</td>
</tr>
<tr>
<td>04</td>
<td>10-Oct-2007</td>
<td>Site (Japan) specific - This amendment was written to include language to comply with local regulatory requirements related to ethics, investigational product, safety information, and administration, and to clarify roles and responsibilities of Investigators and study-related personnel in Japan.</td>
</tr>
<tr>
<td>05</td>
<td>07-Nov-2007</td>
<td>This Amendment serves as Month 2 biomarker sub-study protocol. It describes the study design, data collection, and statistical analysis for the data collected in the sub-study.</td>
</tr>
<tr>
<td>06</td>
<td>07-Mar-2008</td>
<td>Site (France) specific - identical to Amendment 02 but for the French protocol.</td>
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### 2.5 Safety Monitoring

Ongoing blinded monitoring of safety will be conducted by regulatory and medical representatives at BMS and PPD.

In accordance with local regulations, BMS will notify investigators of all SAEs that are unexpected (i.e., not previously described in the Investigator Brochure), and certainly, probably, or possibly related to the investigational product or that could be associated with the study procedures. This notification will be in the form of an expedited safety report (ESR). Upon receiving such notices, the investigator must review and retain the notice with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. Suspected serious adverse reactions shall be reported to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited cases or in aggregate reports).
Any unexpected study outcome event that results in death will be reported as an ESR. However, non-fatal SAEs which are study outcomes will not be reported by BMS as ESRs to study Investigators, health authorities, or IRB/EC. Events that will not be reported by BMS as an ESR include:

- ischemic stroke
- hemorrhagic stroke
- systemic embolism
- major bleeding events
- myocardial infarction

An independent DMC will review on a regular basis, and whenever necessary, efficacy and safety data from the ongoing trial, including the above events and all SAEs reported to the Sponsor. The conduct of the DMC for this study is described in detail in the DMC Charter.

3 OBJECTIVES

3.1 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) and systemic embolism, in subjects with AF and at least one additional risk factor for stroke.

3.2 Secondary Objectives

The key secondary objectives are 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 (ischemic or hemorrhagic) and systemic embolism,
- major bleeding (ISTH)
- all-cause death

Other secondary objectives are:

- 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 naïve 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

- 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.

4 ENDPOINTS

4.1 Efficacy

Only events confirmed by the adjudication committee will be included in the efficacy analyses.

4.1.1 Primary Efficacy Outcome

The primary efficacy endpoint is the time from randomization to first occurrence of confirmed ischemic stroke, hemorrhagic stroke or systemic embolism.

4.1.2 Secondary Efficacy Outcomes

The secondary efficacy endpoints are the time from randomization to first occurrence of confirmed:

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

- composite of stroke (ischemic, hemorrhagic or of unspecified type), systemic embolism, or major bleeding in warfarin naïve subjects

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

Individual components of the primary efficacy endpoint will also be summarized.

4.1.3 Efficacy Outcomes Definition

All suspected efficacy events will be reported as either an AE or a Serious AE (SAE) and will be adjudicated by the Clinical Events Committee (CEC). The endpoints of death, stroke, systemic embolism and myocardial infarction (MI) are defined in the CEC charter.

4.2 Safety

4.2.1 Primary Safety Outcome

The primary safety endpoint is the time from first dose of study drug to first occurrence of confirmed major bleeding during the Treatment Period. The ISTH guidelines (refer to CEC charter) will be used to adjudicate the primary safety endpoint.

4.2.2 Secondary Safety Outcomes

The secondary safety endpoints are the time from first dose of study drug to first occurrence of:

• composite of confirmed (per ISTH guidelines) major bleeding and clinically relevant non-major bleeding during the Treatment Period
• all bleeding events reported by the Investigator during the Treatment Period.
4.2.3 Tertiary Safety Outcomes

Other safety outcome measures will also be assessed, and will include adjudicated bleeding events using GUSTO and TIMI guidelines (refer to CEC charter), fractures, other AEs, vital signs, electrocardiograms (ECGs) and abnormal standard clinical laboratory test results (see Appendix 1 for laboratory MA criteria).

4.2.4 Safety Outcomes Definition

All suspected bleeding events will be reported as either an AE or a Serious AE (SAE). Bleeding events that seem to qualify as major or clinically relevant non-major bleeding using the ISTH guidelines will be adjudicated by the CEC. These bleeding events will be adjudicated to determine whether they fit the following criteria:

- major, clinically relevant non-major or minor bleeding, per ISTH guidelines
- severe, moderate or mild bleeding, per GUSTO guidelines
- major or minor bleeding, per TIMI guidelines.

The bleeding-related endpoints are defined in the CEC charter according to each one of the ISTH, GUSTO and TIMI guidelines.

5 SAMPLE SIZE AND POWER

The primary efficacy endpoint is the time from randomization to first occurrence of confirmed ischemic stroke, hemorrhagic stroke 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. This objective will be addressed by testing the following hypothesis:

\[ H_0 : \text{RR} \geq \Delta \]

versus

\[ H_1 : \text{RR} < \Delta, \]

where RR represents the risk of apixaban relative to warfarin as measured by the hazard ratio. A key aspect of developing the adequate sample size for this trial is arriving at the appropriate non-inferiority (NI) margin. Warfarin has been studied in 6 different placebo controlled randomized trials in subjects with AF. These studies are described by J.
Lawrence (FDA Statistical Reviewer for ximelagatran NDA) along with the details of a meta-analysis for the studies. Following that methodology a 64% relative risk reduction was identified in favor of warfarin for the primary outcome of this trial (lower bound of two-sided 95% confidence interval (CI) for relative risk reduction = 47%). This allowed us to calculate the excess risk due to placebo versus warfarin at 2.78 (lower bound of two-sided 95% CI for this excess risk = 1.88). In order to show that apixaban preserves at least some of the warfarin benefit, one must then show that the upper bound of a two-sided CI for the relative risk of apixaban versus warfarin does not exceed 1.88. However, it is more clinically relevant and conventional to choose a more stringent margin of NI and we have designed this trial with 90% power to show that apixaban maintains at least half of a conservative estimate of the historical benefit of warfarin relative to placebo. To do this, the upper limit of a two-sided CI for the relative risk of apixaban versus warfarin must be less than 1.44.

The apixaban indication for prevention of stroke in AF subjects may be supported by this single pivotal trial. Different regulatory agencies have different requirements for such a regulatory submission. Some agencies require a more stringent control of the type I error (one-sided 0.005 level rather than one-sided 0.025 level) in the presence of a single registrational trial. Others require a more stringent NI margin (1.38 rather than 1.44). Therefore,

(A) in regulatory regions requiring a more stringent NI margin, the NI of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 95% CI for RR is less than 1.38; this corresponds to maintenance of at least half of a conservative estimate of the historical benefit, if that benefit is measured on a logarithmic scale rather than an untransformed scale;

(B) in regulatory regions requiring a more stringent control of the type I error, the NI of apixaban relative to warfarin will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.

The number of events required to achieve 90% power and meet the criteria described in (A) is lower than the number of events required to achieve 90% power and meet the criteria described in (B). This study is sized to meet the more stringent criterion. With 448 subjects with confirmed strokes or systemic emboli, the study will have at least 90% power to meet both regulatory definitions of NI described above.

11-May-2010
Amendment 7 (refer to Section 2.4) increased the sample size of the study from 15,000 to 18,000 subjects. As described in Section 2.1 the trial is event driven (the power of the study does not depend on the number of subjects or the duration of follow-up) and the number of subjects and the length of follow-up required to achieve 448 primary efficacy events in the original protocol were best estimates based on event rates observed in similar trials. Originally the number of subjects and the average length of follow-up required to achieve 448 events were calculated assuming an event rate of 1.67 per hundred subject-years. Prior to the implementation of Amendment 7 monthly reviews of blinded aggregate data for the study showed that primary efficacy events were being accrued at a rate of approximately 1.20 events per hundred subject-years. With the originally planned number of subjects, this lower rate would translate into a longer duration of trial than originally planned to accrue the required number of primary efficacy events (average follow-up would need to be increased from 1.8 years to 2.5 years). Therefore, the sample size was increased from 15,000 to 18,000 subjects without changing the target number of primary efficacy events in the trial.

Based on a revised sample size of 18,000 subjects allocated in a 1:1 ratio to the apixaban or warfarin group, assuming a primary efficacy endpoint rate of 1.20 per hundred subject-years, an average follow-up of ~2.1 years is estimated to be required to accrue the target number of primary efficacy events. These calculations assume an incidence of 1% loss to follow-up.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

In all statistical tabulations, the term “Intended Treatment Period” refers to the period that starts on the day of randomization and ends at the efficacy cut-off date. The efficacy cut-off date will be determined and documented prior to unblinding the study. The Intended Treatment Period will be the basis for the summaries of efficacy.

In all statistical tabulations, the term “Treatment Period” refers to a period that includes measurements or events with onset from first dose of blinded study drug through:

- 2 days after the last dose of blinded study drug when summarizing
bleeding endpoints
bleeding-related serious or non-serious AEs
laboratory, vital signs or ECG measurements

- 30 days after the last dose of blinded study drug when summarizing
  - deaths as an outcome of an SAE
  - SAEs
- 2 days (for non-serious AEs) or 30 days (for SAEs) after the last dose of double-blind study drug when summarizing
  - LFT-related AEs or neurologic AEs
  - overall AEs

This period will be the basis for the summaries of safety.

In all statistical tabulations, the term “Follow-up Period” refers to the period starting after the “Treatment Period” ends through 30 days after discontinuation of study drug (applicable only to subjects who receive at least one dose of study drug).

### 6.2 Treatment Regimens

Efficacy endpoints will be summarized according to the As Randomized group. Subjects (regardless of whether or not they receive blinded study drug) are categorized to the group to which they are assigned by the IVRS.

Safety endpoints will be summarized according to the As Treated group. Subjects who receive at least one dose of blinded study drug are categorized to the group to which they are assigned by the IVRS unless the same incorrect treatment is received throughout the study, in which case the treatment group will be equal to the treatment received.

### 6.3 Populations for Analysis

The following populations will be used for analysis.

**Enrolled Population**: consists of all subjects who signed informed consent.

**Randomized Population**: is a subset of the Enrolled Population consisting of all randomized subjects who signed informed consent. When summarizing data using this population, subjects are categorized according to the As Randomized group.
**Treated Population:** is a subset of the Enrolled Population consisting of all subjects who received at least one dose of blinded study drug and signed informed consent. When summarizing data using this population, subjects are categorized to the **As Treated** group.

**Evaluable Population:** is a subset of the Randomized Population excluding subjects with protocol deviations expected to affect the primary efficacy endpoint (see Section 7.2). In the case of treatment assignment error, the data collected up to the start of incorrect treatment will be included. When summarizing data using this population, subjects are categorized to the **As Randomized** group.

### 7 STATISTICAL ANALYSES

Prior warfarin/VKA status (experienced, naïve) will be included as a stratification factor in some of the efficacy (Section 7.5) and safety analyses (Section 7.6) as well as when summarizing demographic and baseline characteristics (Section 7.3) and extent of exposure (Section 7.4). A subject 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. The stratum associated with each subject will be derived from information entered into the CRF.

#### 7.1 General Methods

All analyses will be performed in SAS® using version 8.2 or higher. Unless otherwise stated, all hypothesis tests will be performed using two-sided tests at the 5% significance level.

Continuous variables will be summarized using descriptive statistics including means, standard deviations, minima, maxima and quartiles, and qualitative or discrete variables will be summarized using absolute and relative frequencies.
**Time to Event Analyses**

Calculation of p-values and construction of point estimates and CIs for RR will be based on Cox proportional hazard models. Site and prior warfarin/VKA status will be included in the model as stratification factors. Additional covariates may be included as described in Sections 7.5 and 7.6. Ties will be handled using Breslow’s methodology.\(^8\)

Rule for combining investigative site:

a) The study includes > 1,000 investigative sites, most randomizing both experienced and naive subjects, leading to a total of > 1,800 possible strata if both prior warfarin/VKA status and actual investigative site are included as stratification factors in the model.

b) The study includes 40 countries randomizing both experienced and naive subjects, leading to a total of 80 possible strata if both prior warfarin/VKA status and investigative site pooled to the country level are included as stratification factors in the model

With a target 448 primary efficacy events, the large number of strata in either a) or b) produces very sparse data and, therefore, the baseline hazard within each stratum would be poorly estimated with such models. For this reason, when using a Cox proportional hazards model stratified by prior warfarin/VKA status and investigative site, site will be pooled to the Geographic Region level.

Event rates will be estimated and plotted over time using Kaplan-Meier methodology.

**Testing Strategy**

A hierarchical testing strategy will be followed:

- NI for the primary efficacy endpoint will be assessed first (refer to Section 5 for NI margins and significance levels associated with this assessment)
- If NI for the primary efficacy endpoint (using a NI margin of 1.38) is demonstrated, then superiority for the primary efficacy endpoint will be tested at the one-sided \( \alpha = 0.025 \) (with an adjustment for alpha spent in the interim test for superiority; see section 7.6.3)
- If superiority for the primary efficacy endpoint is demonstrated then superiority for major bleeding (primary safety endpoint) will be tested at the one-sided \( \alpha = 0.025 \) (with an adjustment for alpha spent in the interim test for superiority associated with the primary efficacy endpoint).
• If superiority for major bleeding is demonstrated then superiority for all-cause death will be tested at the one-sided $\alpha = 0.025$ (with an adjustment for alpha spent in the interim test for superiority associated with the primary efficacy endpoint).

### 7.2 Study Conduct

Significant protocol deviations will be identified for all subjects who are randomized. Significant Protocol Deviation Criteria expected to affect the primary efficacy endpoint are as follows:

- Compliance with apixaban/apixaban placebo $< 80\%$ (see Section 7.4.1 for definition of compliance)
- Subject randomized but not dosed
- Error in treatment assignment resulting in a subject being dosed with an incorrect treatment

All significant protocol deviations including eligibility deviations and use of prohibited concomitant medications will also be listed and summarized by deviation type and randomized treatment group. These summaries will further be tabulated by prior warfarin/VKA status.

### 7.3 Study Population

#### 7.3.1 Subject Disposition

The number of subjects enrolled into the study, and the number of subjects enrolled but not randomized together with the reasons for not being randomized will be summarized. The reasons for not being randomized will be taken from the CRF pre-randomization status page.

The summaries described below will also be presented by prior warfarin/VKA status.

The number of randomized subjects and the number of subjects discontinuing during each study period (treatment period or follow-up period) together with the reasons for discontinuation will be summarized by treatment group. The reasons for discontinuation will be taken from the end-of-treatment and the end-of-follow-up status pages of the CRF. Discontinuations from study drug due to AEs will further be summarized by the AE type: bleeding, stroke, systemic embolism or myocardial infarction.
The frequency of subjects enrolled in each country and in each site will be tabulated by randomized treatment group and for all randomized subjects combined.

7.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by randomized treatment group, using both the Randomized Population and the Evaluable Population. All summaries will be further tabulated by prior warfarin/VKA status. Quantitative variables will be summarized using means, standard deviations, minima, maxima and quartiles, and categorical variables will be summarized using absolute and relative frequencies.

The following demographic and baseline characteristics will be summarized:

- Apixaban dose at randomization (2.5 mg BID or matching placebo, or 5 mg BID or matching placebo)
- Geographic region (refer to Appendix 2)
- Country
- Age
- Age group (< 65, 65-<75, ≥75 years)
- Gender
- Race
- Ethnicity
- Weight
- Weight group (≤ 60, > 60 kg)
- Body mass index (BMI)
- BMI group (≤ 28, >28 to 33, > 33 kg/m²)
- Waist circumference
- Height
- Vital signs
- Level of renal impairment (severe, moderate, mild, normal based on the CrCL value)
- Number and type of baseline risk factors (as collected in the Inclusion Criteria module of the CRF at enrollment)
- CHADS2 score at baseline
- Onset of atrial fibrillation (<3 months, 3 months to 1 year, or >1 year prior to randomization)
• Rhythm at enrollment (atrial fibrillation, atrial flutter, sinus rhythm or appeared to be only on paced rhythm)
• Smoking status (current smoker, former smoker, or never smoked)
• Bleeding history: location and time of last episode for each location (within 1 year of enrollment or more than 1 year ago).

The frequency of subjects receiving selected concomitant medications on the day of randomization will be summarized by medication class (including anti-platelet, anti-coagulant/VKA, lipid lowering, CYP3A4 inhibitor, NSAID).

The frequency of subjects with abnormal baseline physical examination findings will be summarized by examination criteria (as collected in the Physical Examination module of the CRF at enrollment).

Additional frequency tabulations will be presented for other baseline characteristics including those related to history of atrial fibrillation, cardiovascular disease, cerebrovascular disease, thromboembolic events, non-traumatic fractures, and alcohol use (as collected in the History and Habits modules of the CRF at enrollment).

Any imbalances between treatment groups for the characteristics described above will be assessed when reviewing the summary tabulations and any differences deemed clinically relevant to the safety or efficacy comparisons may be investigated by controlling for the characteristic in a supplemental analysis (see Sections 7.5 and 7.6).

7.4 Extent of Exposure

7.4.1 Study Therapy

The summaries described below will be tabulated for the Treated Population. All summaries will be tabulated by treatment group and by treatment group and prior warfarin/VKA status.

Length of exposure to study drug is defined as the number of days the subject is known to be on active study drug. The distribution of the length of exposure to study drug will be presented by treatment group; this distribution will be presented separately by taking into account interruptions of more than 2 consecutive doses and by not taking into account interruptions. The distribution categories will be <1, 1 to <4, 4 to <26, 26 to <52, 52 to
The length of exposure to study drug will also be summarized by treatment group using means, standard deviations, medians, minima and maxima. The total patient-months of exposure to study drug (say, $T$) will be presented for each treatment group and is defined as:

$$\frac{12}{365.25} \sum_{i=1}^{N_T} \text{Length of exposure (days) for subject } i,$$

where $N_T$ represents the number of subjects receiving treatment $T$.

The frequency of subjects experiencing dose interruptions for 5 or more consecutive days at any time during the study together with the reasons for interruptions will be summarized.

Treatment compliance (TC) will be summarized for apixaban/apixaban placebo. The TC will be calculated using the following formula (assuming that either on the first day or the last day subjects only receive one dose):

$$TC = \frac{\text{number of tablets taken}}{(\text{Number of days from first to last dose of blinded study drug} - 1) \times 2 + 1} \cdot 100\%$$

The frequency of subjects with at least 80% compliance with apixaban/apixaban placebo will also be summarized.

### 7.4.2 INR Control

The summaries described below will be tabulated for the Randomized Population. All summaries will be tabulated by treatment group, by treatment group and country and by treatment group and prior warfarin/VKA status.

For subjects who receive warfarin, INR control is a more appropriate measure of compliance than pill count. The assessment of INR control will be based on all available INR values.
For subjects randomized to apixaban, sham (in addition to actual) INR values will be summarized and displayed graphically to assess the performance of the sham algorithm.

INR values will be summarized by visit (see Sections 8.3 and 8.4). These summaries will also be graphically displayed using a box plot.

The proportion of time (counted from first INR value recorded on or after dosing on Day 4 until the day of discontinuation of study drug without considering interruptions) in which subjects have an INR in the following ranges will be summarized:

- INR < 2.0, 2.0 ≤ INR ≤ 3.0, INR > 3.0
- INR < 0.8, 0.8 ≤ INR < 1.8, 1.8 ≤ INR < 2, 2 ≤ INR ≤ 3, 3 < INR ≤ 3.2, 3.2 < INR ≤ 5, 5 < INR ≤ 12, INR > 12

The frequency of subjects with INR in the 2.0-3.0 range for ≥ 60%, ≥ 65%, ≥ 70%, ≥ 75%, or ≥ 80% of time will also be summarized.

Only subjects who have received study drug for at least 4 days will be included in these time-related summaries.

The INR control measure, proportion of time in each INR interval, is calculated using Rosendaal’s method which assumes that the INR value between two measurements varies linearly from the first value to the second value.\(^9\)

- let INR\(_i\) and INR\(_{i+1}\) be the two consecutive INR values
- let D\(_i\) and D\(_{i+1}\) be the dates associated with these two consecutive INR values, \([\{(D_{i+1} - D_i) = k, k > 1\}]
- assuming the linear increase or decrease between the two consecutive INR measurements, the unit change per day in INR is \(m = (\text{INR}_{i+1} - \text{INR}_i) / (D_{i+1} - D_i)\)
- the estimated INR value for the date after D\(_i\) (D\(_{i+1}\)) will be INR\(_i\) + \((m*1)\)
- likewise, the estimated INR value for the date (D\(_{i+2}\)) will be INR\(_i\) + \((m*2)\), etc.; the estimated INR value on the date immediately prior to D\(_{i+1}\) will be INR\(_i\) + \((m*(k-1))\).

Using Rosendaal’s method, each subject will have an INR measurement every day, either actual or by estimation through linear interpolation. The proportion of time subjects have an INR within an interval is the number of days with INR in the interval divided by the total number of days.
7.4.3 Concomitant Medications

The summaries described below will be tabulated for the Treated Population. All summaries will be tabulated by treatment group and by treatment group and prior warfarin/VKA status.

The frequency of subjects receiving concomitant medications after randomization will be summarized by treatment group, medication class (anti-platelet, anti-coagulant/VKA, anti-arrhythmic, diuretic, ace inhibitor, beta blocker, alpha blocker, calcium channel blocker, ARB, lipid lowering, CYP3A4 inhibitor, hypoglycemic, anti-depressant, NSAID, other) and drug name.

The length of exposure to anti-platelets and to anti-coagulants or VKAs administered concomitantly with blinded study drug will be summarized (using means, standard deviations, medians, minima and maxima) by treatment group. The summaries will be presented by medication class and drug name.

7.5 Efficacy

Primary censoring scheme: 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. Efficacy endpoints reached after this cut-off will be summarized by treatment group and by treatment group and prior warfarin/VKA status. Conclusions regarding NI or superiority will be based on the results of the analyses using this censoring scheme.

Supportive censoring schema:

a) subjects who do not experience an efficacy endpoint event from first through 30 days after the last dose of study drug 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 30 days following discontinuation of study drug. This censoring scheme will be used for sensitivity analyses when using the Evaluable Population for the NI test.

b) subjects who do not experience an efficacy endpoint event from first through 2 days after the last dose of study drug 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 2 days following
discontinuation of study drug. This censoring scheme will be used for sensitivity analyses when using the Evaluable Population for the NI test.

The efficacy cut-off date will be determined prior to database lock at a time point when sufficient information is available to estimate the timing of attainment of 448 confirmed primary efficacy events using information such as the observed event rate and the proportion of events that are being confirmed by adjudication.

7.5.1 Analysis of Primary Efficacy Endpoint

7.5.1.1 NI and Superiority Tests

All analyses described in this section will be performed on the Randomized Population using the Primary Censoring scheme.

The primary objective of the study is to demonstrate that apixaban is NI to warfarin for the primary efficacy endpoint. As noted in Section 5, different regulatory agencies have different requirements for demonstrating NI:

(A) in regulatory regions for which the criterion requires testing at one-sided 0.025 significance level and a NI margin of 1.38, NI will be demonstrated if the upper bound of the two-sided 95% CI for RR is less than 1.38;

(B) in regulatory regions for which the criterion requires testing at one-sided 0.005 significance level and a NI margin of 1.44, NI will be demonstrated if the upper bound of the two-sided 99% CI for RR is less than 1.44.

Tests using each NI margin and significance level as described above will be performed using a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin/VKA status. The treatment effect will be measured by the estimated RR and the two-sided CIs for RR. The proportional hazards assumption will be checked by examining the plots of the log(-log(survival)) versus survival time for each stratum included in the Cox proportional hazards model. The proportional hazards assumption will also be tested by assuming that the hazard ratio is constant within each of four time periods, 0-<9 months, 9-<18 months, 18-<27 months, 27 months or more, but will be allowed to vary between these four time periods. The four hazard ratios will be compared using a Wald test.
If the NI criterion described in (A) is met (regardless of whether or not the criterion described in (B) is met), then superiority of apixaban relative to warfarin for the primary efficacy endpoint will be tested at the one-sided 0.025 significance level (with an adjustment for alpha spent in the interim test for superiority; see section 7.6.3) using the same Cox proportional hazards model. Superiority of apixaban will be demonstrated if the calculated p-value is less than the significance level adjusted for the interim test.

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of confirmed stroke (ischemic, hemorrhagic or of unspecified type) or systemic embolism, by treatment group, and by treatment group and prior warfarin/VKA status. Event rates for each of the components of the primary efficacy endpoint will also be estimated by treatment group and by treatment group and prior warfarin/VKA status.

Events that occur after the efficacy cut-off date will be listed.

7.5.1.2 Sensitivity Analysis

To assess the impact of relevant protocol deviations on the NI assessment, the NI tests (using the methodology described in Section 7.5.1.1) will also be performed on the Evaluable Population using each of the Supportive Censoring schema described in Section 7.5 (On Treatment analyses).

Confirmatory analyses will be performed using a Cox proportional hazards model stratified by investigative site and prior warfarin/VKA status with terms for treatment group, a covariate (each of age category (<75, ≥75 yrs), history of stroke, TIA or non-systemic embolus, history of diabetes mellitus, and on treatment for systemic hypertension at randomization) and treatment by covariate interaction. The calculated p-value, estimated RR and two-sided 95% and 99% CIs will be reported. This assessment will be based on the Randomized Population using the Primary Censoring scheme.

Demographic and baseline characteristics for which imbalances between treatment groups are observed and deemed clinically relevant for the efficacy comparisons will be identified (see Section 7.3.2). If such imbalances are observed, the relevant demographic or baseline characteristics will also be included as covariates in a supplemental Cox proportional hazards model. This will allow for the assessment of the importance of these
imbalances on the treatment comparisons. This assessment, if performed, will be based on the Randomized Population using the Primary Censoring scheme.

### 7.5.1.3 Subgroup Analyses

All analyses described in this section will be performed on the Randomized Population using the Primary Censoring scheme.

Table 7.5.1.3 shows the subgroups of interest for analyses of efficacy data. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis.

<table>
<thead>
<tr>
<th>Grouping Variable</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior warfarin/VKA status</td>
<td>Experienced&lt;br&gt;Naive</td>
</tr>
<tr>
<td>Apixaban dose</td>
<td>2.5 mg BID or matching placebo&lt;br&gt;5 mg BID or matching placebo</td>
</tr>
<tr>
<td>Geographic Region</td>
<td>North America&lt;br&gt;Latin America&lt;br&gt;Europe&lt;br&gt;Asia/Pacific</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 65 years old&lt;br&gt;≥ 65 to &lt; 75 years old&lt;br&gt;≥ 75 years old</td>
</tr>
<tr>
<td>Gender</td>
<td>Male&lt;br&gt;Female</td>
</tr>
<tr>
<td>Race</td>
<td>White&lt;br&gt;Black or African American&lt;br&gt;Asian&lt;br&gt;Other</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic/Latino&lt;br&gt;Not Hispanic/Latino</td>
</tr>
<tr>
<td>Weight</td>
<td>≤ 60 kg&lt;br&gt;&gt; 60 kg</td>
</tr>
</tbody>
</table>
Table 7.5.1.3: Subgroups of Interest for Efficacy Assessments

<table>
<thead>
<tr>
<th>Grouping Variable</th>
<th>Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Renal Impairment</td>
<td>Severe or Moderate</td>
</tr>
<tr>
<td></td>
<td>- Mild</td>
</tr>
<tr>
<td></td>
<td>- Normal</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td>≤ 1</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
</tr>
<tr>
<td>CHADS2 Score</td>
<td>≤ 1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
</tr>
<tr>
<td>Prior Stroke or TIA</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Hypertension requiring pharmacological treatment</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Aspirin at randomization</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

Other subgroups of clinical relevance may be added as appropriate.

Each of these subgroups will be analyzed using a Cox proportional hazards model stratified by prior warfarin/VKA status (not applicable for the first subgroup listed) with terms for treatment group. The estimated RR and two-sided 95% CI will be calculated to assess the treatment effect within each of the subgroups. The p-value for the test of the treatment by grouping variable interaction will be presented based on a Cox proportional hazards model stratified by prior warfarin/VKA status (not applicable for the first subgroup listed) with terms for treatment group, the grouping variable and treatment by grouping variable interaction.
Event rates within each subgroup will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of confirmed stroke (ischemic, hemorrhagic or of unspecified type) or systemic embolism, by treatment group.

### 7.5.2 Analysis of Secondary Efficacy Endpoints

All analyses described in this section will be performed on the Randomized Population using the Primary Censoring scheme.

For each of the secondary efficacy endpoints listed in Section 4.1.2, a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and, when applicable, prior warfarin/VKA status will be used to estimate RR and two-sided 95% CIs for RR.

Following the sequential testing strategy outlined in Section 7.1, if superiority for the primary safety endpoint (major bleeding) is demonstrated at the one-sided 0.025 significance level (with an adjustment for alpha spent in the interim test for superiority; see section 7.6.3) then superiority of apixaban relative to warfarin for all-cause death will be tested at the one-sided 0.025 significance level (with an adjustment for alpha spent in the interim test for superiority). For all other secondary efficacy endpoints, nominal two-sided p-values associated with a test of $H_0: \text{RR}=1$ vs $H_1: \text{RR} \neq 1$ will be calculated.

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of any of the components of each secondary efficacy endpoint, by treatment group and by treatment group and prior warfarin/VKA status.

All confirmed efficacy events (death, ischemic stroke, hemorrhagic stroke, unspecified stroke, systemic embolism, myocardial infarction) will be listed, indicating the subject id, randomized treatment group, age, gender, race, date of last dose of study drug prior to event and day of event relative to start of dosing. The time of death and cause of death will also be included in the listing of deaths.

### 7.6 Safety

All analyses described in this section will be performed on the Treated Population.
Censoring scheme for time to event analyses of bleeding endpoints: subjects who do not experience a bleeding endpoint will be censored at the earlier of 2 days after discontinuation of study drug, death date, or last-contact date (for subjects who withdraw consent to be followed up or are lost to follow-up) at the end of the study.

7.6.1 Primary Safety Analysis

Following the sequential testing strategy outlined in Section 7.1, if superiority for the primary efficacy endpoint is demonstrated at the one-sided 0.025 significance level (with an adjustment for alpha spent in the interim test for superiority; see section 7.6.3) then superiority of apixaban relative to warfarin for major bleeding (ISTH) will be tested at the one-sided 0.025 significance level (with an adjustment for alpha spent in the interim test for superiority).

A Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and prior warfarin/VKA status will be used to estimate RR and two-sided 95% CIs for RR.

Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from first dose to first occurrence of confirmed major bleeding (ISTH), by treatment group and by treatment group and prior warfarin/VKA status.

Subgroup analyses for the primary safety endpoint will be performed as described for the primary efficacy endpoint.

7.6.2 Secondary Safety Analysis

7.6.2.1 Bleeding Endpoints

For each of the secondary safety endpoints listed in Section 4.2.2 and for the bleeding endpoints (using the GUSTO or TIMI definitions) listed in Section 4.2.4, a Cox proportional hazards model including treatment group as a covariate and stratified by investigative site and, when applicable, prior warfarin/VKA status will be used to estimate RR and two-sided 95% CIs for RR.
Event rates will be estimated and Kaplan-Meier curves will be plotted for the time from randomization to first occurrence of any of the components of each secondary safety endpoint, by treatment group and by treatment group and prior warfarin/VKA status.

Subgroup analyses for the bleeding safety endpoints will be performed as described for the primary efficacy endpoint.

All confirmed bleeding events (adjudicated per ISTH, GUSTO and TIMI guidelines) will be listed, indicating the subject id, treatment group, age, gender, race, date of last dose of blinded study drug prior to event and day of event relative to start of dosing.

7.6.2.2 Adverse Events

All AEs are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). Listings and summaries will be based on the resulting SOCs and PTs.

Analysis of all safety data will follow the BMS safety data conventions (described in “Analysis of Safety Data - Reference to CT SOP 109”)

All reported AEs and SAEs will be listed, indicating the subject id, treatment group, age, gender, race, day of onset relative to start of dosing, resolution date, investigator-assessment of relationship to study drug, investigator-assessment of intensity of event, action taken regarding study drug and whether treatment was required for the event.

Summary information (the number and percentage of subjects) regarding AEs (for serious and non-serious events) will be tabulated by SOC, PT and treatment group for:

- deaths (outcome of an SAE)
- SAEs
- most common SAEs (reported in more than 1% of subjects in any treatment group)
- bleeding-related AEs (serious or non-serious)
- AEs (serious or non-serious) related to LFT increases
- Neurologic AEs (serious or non-serious)
- AEs leading to study drug discontinuation
- related AEs
- related events categorized by intensity
• all AEs (serious or non-serious)
• most common (serious or non-serious) AEs (reported in more than 5% of subjects in any treatment group)

Laboratory AEs are laboratory results identified by the Investigator as AEs and thus reported on the AE pages of the CRF. Any such AE will be included in the respective AE summaries.

7.6.2.3 Laboratory Data

Laboratory measurements and their changes from baseline will be summarized by nominal visit and treatment group, for protocol specified analytes. The frequency of subjects with laboratory marked abnormalities (MAs) during the Treatment Period based on pre-specified criteria (see Appendix 1) will be tabulated by treatment group, for each analyte.

Shift analysis will be performed to evaluate qualitative changes that occurred during treatment. For protocol specified analytes, shift tables will display, by treatment group, the frequency of subjects with the following combination of values at baseline and post-dose during the Treatment Period:

• no change (low to low: L-L, normal to normal: N-N, high to high: H-H)
• abnormal to normal (low to normal: L-N, high to normal: H-N)
• normal to abnormal (normal to low: N-L, normal to high: N-H)
• abnormal to abnormal (low to high: L-H, high to low: H-L),

where low refers to values that are < LLN, high refers to values that are > ULN and normal refers to values in-between the normal limits (including the limits). Two shift tables will be presented:

• one for labs with MA criteria based on high values (regardless of whether the MA criteria also considers low values) - the post-dose value considered for the tabulation will be the largest value obtained during the Treatment Period;
• another for labs with MA criteria based on low values (regardless of whether the MA criteria also considers high values) - the post-dose value considered for the tabulation will be the smallest value obtained during the Treatment Period.

The following considerations apply to the tabulations described below:
- elevations refer to values that meet the specified criterion and are larger (as multiples of ULN) than the baseline value
- decreases refer to values that meet the specified criterion and are smaller than the baseline value
- values will be counted towards the categories of “AST and ALT elevations” or “AT and Total Bilirubin elevation” if both AST and ALT or both AT and Total Bilirubin, respectively, meet the criterion and at least one of the values in the component is larger than the baseline value
- values will be counted towards the categories of “AST or ALT elevations” if either AST meets the criteria and is larger than the AST baseline value or ALT meets the criterion and is larger than the ALT baseline value.
- if the baseline value is missing then all values for that particular lab that meet the criterion will be included in the tabulation
- for each subject and lab or lab combination, the largest (for LFTs; largest as multiples of ULN) or the smallest (for platelet counts) post-dose measurement during the analysis period will be counted for the post-dose summaries that do not take into consideration visit
- for each subject and lab or lab combination, the largest (for LFTs; largest as multiples of ULN) or the smallest (for platelet counts) post-dose measurement within each visit window will be counted for the post-dose summaries by nominal visit.

Decreases in platelet counts, increases in liver-related elevations, discontinuations and deaths will be tabulated by treatment group during the Treatment Period and during the Follow-up Period. The tabulations will include the number and proportion of subjects with

- AST elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- AST or ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- Both AST and ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN on the same date.
- Total bilirubin elevations > 1.5×ULN or >2×ULN
- AT (ALT or AST) elevations >3×ULN and total bilirubin elevations >1.5×ULN on the same date, or AT elevations >3×ULN and total bilirubin elevations >2×ULN on the same date
- ALT elevations >3×ULN and total bilirubin elevations >1.5×ULN on the same date, or ALT elevations >3×ULN and total bilirubin elevations >2×ULN on the same date.
- AT elevations >3×ULN and total bilirubin elevations >2×ULN and ALP <2×ULN on the same date.
Apixaban CV185030
BMS-562247 Statistical Analysis Plan

- ALT elevations >3×ULN and total bilirubin elevations >2×ULN on the same date
- ALP elevations >1.5×ULN
- Platelet counts < 100,000/mm$^3$, or < 50,000/mm$^3$
- liver-related discontinuations
- liver-related deaths.

Similar tabulations will be presented by treatment group and by nominal visit (including baseline).

7.6.2.4 Vital Signs

Vital sign measurements (systolic BP, diastolic BP and heart rate) and their changes from baseline will be summarized by nominal visit and treatment group.

7.6.3 Interim Analysis

A formal interim analysis will be performed once approximately 50% (224) of the primary efficacy endpoint events have been confirmed by the CEC. The objective of this interim analysis will be to determine whether apixaban is superior to warfarin for the primary efficacy endpoint. No interim testing for NI will be performed. As outlined in the DMC charter, the DMC could recommend stopping the study if the one-sided p-value associated with the superiority test for the primary efficacy endpoint is < 0.0001.

The effect of the interim test for superiority on the type I error for the final NI and superiority assessments is described below.

The interim test for superiority for the primary efficacy endpoint and the final analysis test for NI use different null hypotheses. To measure the effect of the interim test for superiority for the primary efficacy endpoint upon the final analysis for NI, the critical values from the interim analysis can be interpreted as critical values from interim tests of the null hypothesis used in the NI analysis. The two sets of critical values are related in the following way:
Critical Value for Testing Superiority | Corresponding Critical Value Expressed as a Test for NI (Approximation a)
--- | ---
$Z_{SUP} < -Z_C$ | $Z_{NI} < -Z_C - \frac{\ln(\Delta)}{\sqrt{4/D}}$

where,

- $Z_{SUP}$ and $Z_{NI}$ are the test statistics for superiority and NI, respectively
- $Z_C$ is the critical value (= 3.719*)
- $\Delta$ is the NI margin ($\Delta$=1.44 or $\Delta$=1.38)
- $D$ is the number of events at the time of the analysis (D= 224*)

* Note that although the interim analysis is planned once 224 primary efficacy events are adjudicated, if a bolus of events were adjudicated at the same time and the target number of 224 is exceeded then the adjustment of type I error for the final test of NI described below will be changed accordingly.

Therefore, the effect of the interim analysis to assess superiority for the primary efficacy endpoint has the following effect on the final tests:

- negligible effect on the type I error for the final assessment of NI ($<5\times10^{-10}$); therefore the final assessment of NI will be performed at
  - (A) one-sided $\alpha=0.025$ when using NI margin of 1.38
  - (B) one-sided $\alpha=0.005$ when using NI margin of 1.44
- an effect $< 0.0001$ on the type I error for the final tests of superiority for the primary efficacy endpoint, the primary safety endpoint and for all-cause death; therefore the final tests of superiority for these endpoints will be performed at one-sided $\alpha = 0.025 - 0.0001 = 0.02499$.

If the study is stopped early based on the result of the interim superiority test, then the hazard ratio estimate will be adjusted as described in Section 10.

Further details regarding interim analyses, including details on interim assessments of safety can be found in the DMC Charter.
7.7 Pharmacokinetics/Pharmacodynamics

The PK/PD analysis plan will be detailed in a separate document.

7.8 Outcomes Research Analysis

The outcomes research analysis plan will be detailed in a separate document.

8 CONVENTIONS

8.1 Safety Data Conventions

Except as noted in Section 7.6, safety data will be handled according to the BMS safety data conventions (described in “Analysis of Safety Data - Reference to CT SOP 109”). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

For the analyses of efficacy and bleeding endpoints, imputation of missing or partial dates for efficacy and bleeding events will follow the convention outlined in “Analysis of Safety Data - Reference to CT SOP 109”, but rather than using the hierarchy “first active study medication date, consent date, visit date corresponding to the visit at which the event was reported”, should instead use the following hierarchy:

- “first active study medication date, randomization date, consent date” for efficacy and bleeding endpoints other than death
- “last contact date” for death.

Other conventions not described in the above mentioned document and which will be used when analyzing data from study CV185030 are described in the following sections.

8.2 Baseline Measurements

For laboratory measures the following will be used, in a hierarchical sequence, to select the baseline (if a criterion does not apply it would be skipped in the sequence):

- the baseline value corresponds to the last lab drawn prior to first dose of blinded study drug;
• if both local and central laboratory values qualify as baseline according to the above criterion, the central laboratory value will be used as the baseline value;
• if more than one value qualifies as baseline according to the above criterion, then the average of such values will be used as the baseline value.

For all other measures the following will be used, in a hierarchical sequence, to select the baseline:
• the baseline value is the last value prior to the first dose of blinded study drug;
• if more than one value qualifies as baseline according to the above criterion, then the average of such values will be used as the baseline value.

8.3 Day Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. The day ranges for the analyses of safety measurements are defined in the following table. Values associated with each nominal visit (except for the follow-up visit) will be considered from first day of dosing until 2 days after discontinuation of study drug.

Table 8.3: Day Ranges for Analysis of INR and Safety Measurements

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Target Day</th>
<th>Day Ranges</th>
<th>Nominal Visit</th>
<th>Target Day</th>
<th>Day Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>Day 4</td>
<td>Post-Baseline Day 1 to Day 5</td>
<td>Month 29</td>
<td>Day 882</td>
<td>Days 867 - 897</td>
</tr>
<tr>
<td>Week 1</td>
<td>Day 7</td>
<td>Days 6 - 8</td>
<td>Month 30</td>
<td>Day 913</td>
<td>Days 898 - 928</td>
</tr>
<tr>
<td>Day 10</td>
<td>Day 10</td>
<td>Days 9 - 12</td>
<td>Month 31</td>
<td>Day 943</td>
<td>Days 929 - 958</td>
</tr>
<tr>
<td>Week 2</td>
<td>Day 14</td>
<td>Days 13 - 17</td>
<td>Month 32</td>
<td>Day 974</td>
<td>Days 959 - 989</td>
</tr>
<tr>
<td>Week 3</td>
<td>Day 21</td>
<td>Days 18 - 25</td>
<td>Month 33</td>
<td>Day 1004</td>
<td>Days 990 - 1019</td>
</tr>
<tr>
<td>Month 1</td>
<td>Day 30</td>
<td>Days 26 - 45</td>
<td>Month 34</td>
<td>Day 1034</td>
<td>Days 1020 - 1049</td>
</tr>
<tr>
<td>Month 2</td>
<td>Day 61</td>
<td>Days 46 - 76</td>
<td>Month 35</td>
<td>Day 1065</td>
<td>Days 1050 - 1080</td>
</tr>
<tr>
<td>Month 3</td>
<td>Day 91</td>
<td>Days 77 - 106</td>
<td>Month 36</td>
<td>Day 1095</td>
<td>Days 1081 - 1110</td>
</tr>
<tr>
<td>Month 4</td>
<td>Day 121</td>
<td>Days 107 - 136</td>
<td>Month 37</td>
<td>Day 1125</td>
<td>Days 1111 - 1140</td>
</tr>
<tr>
<td>Month 5</td>
<td>Day 152</td>
<td>Days 137 - 167</td>
<td>Month 38</td>
<td>Day 1156</td>
<td>Days 1141 - 1171</td>
</tr>
<tr>
<td>Month 6</td>
<td>Day 183</td>
<td>Days 168 - 198</td>
<td>Month 39</td>
<td>Day 1186</td>
<td>Days 1172 - 1201</td>
</tr>
<tr>
<td>Month 7</td>
<td>Day 213</td>
<td>Days 199 - 228</td>
<td>Month 40</td>
<td>Day 1216</td>
<td>Days 1202 - 1231</td>
</tr>
<tr>
<td>Month 8</td>
<td>Day 244</td>
<td>Days 229 - 259</td>
<td>Month 41</td>
<td>Day 1247</td>
<td>Days 1232 - 1262</td>
</tr>
<tr>
<td>Month 9</td>
<td>Day 274</td>
<td>Days 260 - 289</td>
<td>Month 42</td>
<td>Day 1277</td>
<td>Days 1263 - 1292</td>
</tr>
<tr>
<td>Month 10</td>
<td>Day 304</td>
<td>Days 290 - 319</td>
<td>Month 43</td>
<td>Day 1307</td>
<td>Days 1293 - 1322</td>
</tr>
<tr>
<td>Month 11</td>
<td>Day 335</td>
<td>Days 320 - 350</td>
<td>Month 44</td>
<td>Day 1338</td>
<td>Days 1323 - 1353</td>
</tr>
<tr>
<td>Month 12</td>
<td>Day 365</td>
<td>Days 351 - 380</td>
<td>Month 45</td>
<td>Day 1368</td>
<td>Days 1354 - 1383</td>
</tr>
<tr>
<td>Month 13</td>
<td>Day 395</td>
<td>Days 381 - 410</td>
<td>Month 46</td>
<td>Day 1398</td>
<td>Days 1384 - 1413</td>
</tr>
</tbody>
</table>
Table 8.3: Day Ranges for Analysis of INR and Safety Measurements

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Target Day</th>
<th>Day Ranges</th>
<th>Nominal Visit</th>
<th>Target Day</th>
<th>Day Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 14</td>
<td>Day 426</td>
<td>Days 411 - 441</td>
<td>Month 47</td>
<td>Day 1429</td>
<td>Days 1414 - 1444</td>
</tr>
<tr>
<td>Month 15</td>
<td>Day 456</td>
<td>Days 442 - 471</td>
<td>Month 48</td>
<td>Day 1459</td>
<td>Days 1445 - 1474</td>
</tr>
<tr>
<td>Month 16</td>
<td>Day 486</td>
<td>Days 472 - 501</td>
<td>Month 49</td>
<td>Day 1489</td>
<td>Days 1475 - 1504</td>
</tr>
<tr>
<td>Month 17</td>
<td>Day 517</td>
<td>Days 502 - 532</td>
<td>Month 50</td>
<td>Day 1520</td>
<td>Days 1505 - 1535</td>
</tr>
<tr>
<td>Month 18</td>
<td>Day 548</td>
<td>Days 533 - 563</td>
<td>Month 51</td>
<td>Day 1550</td>
<td>Days 1536 - 1565</td>
</tr>
<tr>
<td>Month 19</td>
<td>Day 578</td>
<td>Days 564 - 593</td>
<td>Month 52</td>
<td>Day 1580</td>
<td>Days 1566 - 1595</td>
</tr>
<tr>
<td>Month 20</td>
<td>Day 609</td>
<td>Days 594 - 624</td>
<td>Month 53</td>
<td>Day 1611</td>
<td>Days 1596 - 1626</td>
</tr>
<tr>
<td>Month 21</td>
<td>Day 639</td>
<td>Days 625 - 654</td>
<td>Month 54</td>
<td>Day 1641</td>
<td>Days 1627 - 1656</td>
</tr>
<tr>
<td>Month 22</td>
<td>Day 669</td>
<td>Days 655 - 684</td>
<td>Month 55</td>
<td>Day 1671</td>
<td>Days 1657 - 1686</td>
</tr>
<tr>
<td>Month 23</td>
<td>Day 700</td>
<td>Days 685 - 715</td>
<td>Month 56</td>
<td>Day 1702</td>
<td>Days 1687 - 1717</td>
</tr>
<tr>
<td>Month 24</td>
<td>Day 730</td>
<td>Days 716 - 745</td>
<td>Month 57</td>
<td>Day 1732</td>
<td>Days 1718 - 1747</td>
</tr>
<tr>
<td>Month 25</td>
<td>Day 760</td>
<td>Days 746 - 775</td>
<td>Month 58</td>
<td>Day 1762</td>
<td>Days 1748 - 1777</td>
</tr>
<tr>
<td>Month 26</td>
<td>Day 791</td>
<td>Days 776 - 806</td>
<td>Month 59</td>
<td>Day 1793</td>
<td>≥ Day 1778</td>
</tr>
<tr>
<td>Month 27</td>
<td>Day 821</td>
<td>Days 807 - 836</td>
<td>Follow-up</td>
<td>Last dose</td>
<td>3 to 30 days after</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day + 30</td>
<td>last dose of study</td>
</tr>
<tr>
<td>Month 28</td>
<td>Day 851</td>
<td>Days 837 - 866</td>
<td></td>
<td></td>
<td>drug</td>
</tr>
</tbody>
</table>

Day 1 = First day of dosing with blinded study drug

8.4 Multiple Measurements

INR Values

If multiple INR values are registered in the IVRS within the same nominal visit, the INR value obtained on the day closest to the target day for that nominal visit will be used; in the case of a tie, the measurement obtained at the earlier date and time will be used in the summaries.

Laboratory Measurements

For tabulations of changes from baseline or shift analyses the following will be used, in a hierarchical sequence, to select the post-measurement measurement included in the analysis (if a criterion does not apply it would be skipped in the sequence):

- if multiple laboratory measurements are obtained within the same nominal visit, then the measurement obtained on the day closest to the target day for that nominal visit will be used;
• if more than one value meets the above criterion, then the measurement obtained on the earlier day will be used;
• if both local and central laboratory values meet the above criterion, then the central laboratory value will be used;
• if more than one value meets the above criterion, then the average of such values will be used.

For tabulations of MAs (e.g. ALT > 3xULN), if multiple laboratory measurements are obtained within the same nominal visit or analysis period (post-baseline), then the worst measurement within the nominal visit window or analysis period, respectively, will be used.

**Vital Signs**

The following criteria will be used, in a hierarchical sequence, to select the post-measurement included in the analysis:

• if multiple vital sign measurements are obtained within the same nominal visit, then the measurement obtained on the day closest to the target day for that nominal visit will be used;
• if more than one value meets the above criterion, the measurement obtained on the earlier date/time will be used;
• if more than one value meets the above criterion, then the average of such values will be used.

**9 CONTENT OF REPORTS**

The results of this study will be presented in a standard BMS Clinical Study Report (CSR). Prior to completion of the CSR an Initial Data Assessment will be prepared briefly identifying the key results and any unanticipated findings that are unusual for a study within this program. Prior to completion of the Initial Data Assessment, a meeting for the initial dissemination of study results will be held after database lock and un-blinding. Attendees at this meeting will review all efficacy and safety summaries and listings and will identify key results that should be highlighted in the Initial Data Assessment and CSR.
ADJUSTMENT TO ESTIMATION IN GROUP SEQUENTIAL TESTING AND CONTROLLING TYPE I ERROR RATE IN MULTIPLE ENDPOINTS

The protocol design includes an interim analysis to test superiority of apixaban relative to warfarin after observing confirmed 50% (224) of the planned events. As outlined in DMC charter, the DMC could recommend stopping the study early if the one-sided p-value associated with the superiority test for the primary efficacy endpoint is < 0.0001. This section describes the adjustments to the hazard ratio estimate and CI if the trial is stopped early at the planned interim analysis. It also describes the methodology for testing the secondary endpoints to preserve the overall type I error rate.

10.1 Bias Adjustment for Log Hazard Ratio Estimator

Since early stopping only occurs when interim results are favorable, there is potential for bias in the hazard ratio estimates obtained in a sequentially monitored trial (Jennison and Turnbull 1999)\(^{10}\). A method proposed by Whitehead (1986)\(^{11}\) to obtain a bias adjusted estimator will be used to account for the bias of unadjusted log hazard ratio estimator. This estimator has been shown to have lower mean squared error than an alternative method.\(^{10}\) It is an iterative procedure which uses bias and slope of bias functions to produce an adjusted bias estimator. In this study, simulation results will be used to numerically compute bias and slope of bias functions for a comprehensive set of values over for range of likely hazard ratios. These numerically computed bias and slope of bias will be used to iteratively obtain a bias adjusted estimator of hazard ratio.

10.2 Coverage for Confidence Intervals

It is generally recognized that if CIs are not adjusted for early stopping, there will be inadequate coverage. Jennison and Turnbull\(^{10}\) identify this problem and recommend that naive CIs should not be presented in group sequential testing. To ensure adequate coverage of CIs for the primary efficacy endpoint, CIs will be constructed by inverting hypothesis tests using the stage-wise ordering as described in Jennison and Turnbull.\(^{10}\)
10.3 Adjustment in Type I Error for Testing All Cause Death

In the testing strategy proposed in this study, apixaban is first tested to show non-inferior to warfarin in primary efficacy endpoint. If that test is significant then superiority of apixaban over warfarin is tested. If this test is also significant then a test to show that apixaban is superior to warfarin for all cause death is tested. In this testing strategy, it is likely that the tests of primary efficacy endpoint and all cause death are correlated and type I error level used in final analysis for all cause death maybe inflated than intended significance level. To ensure global control of the type I error in the presence of interim testing, the second method described in Hung, Wang, and O’Neill (2007)\textsuperscript{12} will be used. In this method the critical value for the secondary variable testing is set equal to the corresponding critical value for the primary endpoint.

10.4 Simulation Details

Log hazard ratios from -0.90 to 0.20 will be considered an interval of interest in this study. This corresponds to hazard ratios of 0.41 to 1.22. Initially, to obtain numerical estimates of bias and slope of bias functions, bias will be estimated for log hazard ratios from -2.5 to 1.5 with an increment of 0.0001 to obtain a smooth slope. One-sided p-value of 0.001 boundary (3.719) will be used to determine early stopping at 224 events. If the trial was not stopped early, an adjusted final boundary will be used (1.96014). For each simulation (each value of log hazard ratio) 20,000 estimates will be generated, and point estimate and CIs will be computed for each value. Using these values, bias and 95% CIs will be computed. Hazard ratio (in logarithm form), bias, and slope of bias will be outputted into a data set for correcting bias using method described in Whitehead.\textsuperscript{11}
# APPENDIX 1 LABORATORY MA CRITERIA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Code</th>
<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>HB</td>
<td>g/dL</td>
<td>Low only</td>
<td>Baseline - Value &gt; 2g/dL OR Value ≤ 8 g/dL</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>HCT</td>
<td>%</td>
<td>Low only</td>
<td>Value &lt; 0.75 × Baseline</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>RBC</td>
<td>×10⁶ cells/μL</td>
<td>Low only</td>
<td>Value &lt; 0.75 × Baseline</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>PLAT</td>
<td>×10⁹ cells/L</td>
<td>Low Only</td>
<td>Value &lt; 100 × 10⁹ cells/L (i.e. &lt; 100,000/mm³)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>WBC</td>
<td>×10³ cells/μL</td>
<td>Low/High</td>
<td>LOW if Value &lt; 0.8 × Baseline when Baseline not missing AND Baseline &lt; LLN (of Baseline) OR Value &lt; LLN (of Value) when Baseline not missing AND Baseline &gt; ULN (of Baseline) OR Value &lt; 0.75 × LLN (of Value) when Baseline is missing OR LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIGH if Value &gt; 1.2 × Baseline when Baseline not missing AND Baseline &gt; ULN (of Baseline) OR Value &gt; ULN (of Value) when Baseline not missing AND Baseline &lt; LLN (of Baseline) OR Value &gt; 1.25 × ULN (of Value) when Baseline is missing OR LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
</tr>
<tr>
<td>Neutrophils (absolute)</td>
<td>NEUTA</td>
<td>×10³ cells/μL</td>
<td>Low Only</td>
<td>Value &lt; 1.0 × 10³ cells/μL</td>
</tr>
<tr>
<td>Eosinophils (absolute)</td>
<td>EOSA</td>
<td>×10³ cells/μL</td>
<td>High only</td>
<td>Value &gt; 0.750 × 10³ cells/μL</td>
</tr>
<tr>
<td>Basophils</td>
<td>BASOA</td>
<td>×10³ cells/μL</td>
<td>High only</td>
<td>Value &gt; 0.4 × 10³ cells/μL</td>
</tr>
<tr>
<td>Parameter (absolute)</td>
<td>Test Code</td>
<td>Units</td>
<td>Direction of Change</td>
<td>MA Criteria (applied to Value of labs collected on or after first dose only)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Monocytes (absolute)</td>
<td>MONOA</td>
<td>$10^3$ cells/µL</td>
<td>High only</td>
<td>Value &gt; $2 \times 10^3$ cells/µL (i.e. &gt; 2000/mm$^3$)</td>
</tr>
<tr>
<td>Lymphocytes (absolute)</td>
<td>LYMPA</td>
<td>$10^3$ cells/µL</td>
<td>Low/High</td>
<td>LOW if Value &lt; $0.75 \times 10^3$ cells/µL, HIGH if Value &gt; $7.50 \times 10^3$ cells/µL</td>
</tr>
</tbody>
</table>

**LIVER/KIDNEY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Code</th>
<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase</td>
<td>ALP</td>
<td>U/L</td>
<td>High only</td>
<td>Value &gt; 2 x ULN (ULN is associated to Value being evaluated)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase</td>
<td>AST</td>
<td>U/L</td>
<td>High only</td>
<td>Value &gt; 3 x ULN (ULN is associated to Value being evaluated)</td>
</tr>
<tr>
<td>Alanine Aminotransferase</td>
<td>ALT</td>
<td>U/L</td>
<td>High only</td>
<td>Value &gt; 3 x ULN (ULN is associated to Value being evaluated)</td>
</tr>
<tr>
<td>Bilirubin, Total</td>
<td>TBILI</td>
<td>mg/dL</td>
<td>High only</td>
<td>Value &gt; 2 x ULN (ULN is associated to Value being evaluated)</td>
</tr>
<tr>
<td>Bilirubin, Direct</td>
<td>DBILI</td>
<td>mg/dL</td>
<td>High only</td>
<td>Value &gt; 1.5 x ULN (ULN is associated to Value being evaluated)</td>
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<td>mg/dL</td>
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<td>Creatinine</td>
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<td>Value &gt; 1.5 x ULN (ULN is associated to Value being evaluated)</td>
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**ELECTROLYTES**

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<tbody>
<tr>
<td>Sodium, Serum</td>
<td>NA</td>
<td>mEq/L</td>
<td>Low/High</td>
<td>LOW if Value &lt; 0.95 x Baseline when Baseline not missing AND Baseline &lt; LLN (of Baseline) OR Value &lt; LLN (of Value) when Baseline not missing AND</td>
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<td>Parameter</td>
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<td>Units</td>
<td>Direction of Change</td>
<td>MA Criteria (applied to Value of labs collected on or after first dose only)</td>
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</table>
| Potassium, Serum     | K         | mEq/L   | Low/High            | Low if  
Value < 0.90 × Baseline when 
Baseline not missing AND 
Baseline < LLN (of Baseline) 
OR 
Value < LLN (of Value) when 
Baseline not missing AND 
Baseline > ULN (of Baseline) 
OR 
Value < 0.90 × LLN (of Value) when 
Baseline is missing OR 
LLN (of B) ≤ Baseline ≤ ULN (of B) 

HIGH if  
Value > 1.10 × Baseline when 
Baseline not missing AND 
Baseline > ULN (of Baseline) 
OR 
Value > ULN (of Value) when 
Baseline not missing AND 
Baseline < LLN (of Baseline) 
OR 
Value > 1.10 × ULN (of Value) when 
Baseline is missing OR 
LLN (of B) ≤ Baseline ≤ ULN (of B) |
| Chloride, Serum      | CL        | mEq/L   | Low/High            | LOW if  
Value < 0.90 × Baseline when 
Baseline not missing AND 
Baseline < LLN (of Baseline) 
OR 
Value < LLN (of Value) when 
Baseline not missing AND 
Baseline > ULN (of Baseline) 
OR 
Value < 0.90 × LLN (of Value) when 
Baseline is missing OR 
LLN (of B) ≤ Baseline ≤ ULN (of B) 

HIGH if  
Value > 1.10 × Baseline when 
Baseline not missing AND 
Baseline > ULN (of Baseline) 
OR 
Value > ULN (of Value) when 
Baseline not missing AND 
Baseline < LLN (of Baseline) 
OR 
Value > 1.10 × ULN (of Value) when 
Baseline is missing OR 
LLN (of B) ≤ Baseline ≤ ULN (of B) |
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<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
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<td>Calcium, Total</td>
<td>CA</td>
<td>mg/dL</td>
<td>Low/High</td>
<td>LOW if Value &lt; 0.75 × Baseline when Baseline not missing AND Baseline &lt; LLN (of Baseline) OR Value &lt; LLN (of Value) when Baseline not missing AND Baseline &gt; ULN (of Baseline) OR Value &gt; 0.80 × LLN (of Value) when Baseline is missing OR LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
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<tr>
<td>Bicarbonate</td>
<td>HCO3</td>
<td>mEq/L</td>
<td>Low/High</td>
<td>HIGH if Value &gt; 1.25 × Baseline when Baseline not missing AND Baseline &gt; ULN (of Baseline) OR Value &gt; ULN (of Value) when Baseline not missing AND Baseline &lt; LLN (of Baseline) OR Value &gt; 1.20 × ULN (of Value) when Baseline is missing OR LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
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<td>Units</td>
<td>Direction of Change</td>
<td>MA Criteria (applied to Value of labs collected on or after first dose only)</td>
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<td>Value &lt; 0.75 × Baseline when</td>
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<td>Baseline not missing AND</td>
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<td>Baseline &lt; LLN (of Baseline)</td>
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<td>Baseline is missing OR</td>
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<td>LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
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<tr>
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<td>HIGH if</td>
<td>Value &gt; 1.25 × Baseline when</td>
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<td>Baseline is missing OR</td>
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<td>LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
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**OTHER CHEMISTRY**

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<td>&gt; 5 × ULN</td>
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<td>Total Protein</td>
<td>TPRO</td>
<td>g/dL</td>
<td>Low/High</td>
<td>LOW if</td>
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<td>Value &lt; 0.90 × Baseline when</td>
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<td>Baseline &lt; LLN (of Baseline)</td>
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<td>Value &lt; LLN (of Value) when</td>
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<td>Baseline not missing AND</td>
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<td>Baseline &gt; ULN (of Baseline)</td>
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<td>OR</td>
<td>Value &lt; 0.90 × LLN (of Value) when</td>
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<td>Baseline is missing OR</td>
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<td>LLN (of B) ≤ Baseline ≤ ULN (of B)</td>
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<td>HIGH if</td>
<td>Value &gt; 1.10 × Baseline when</td>
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<td>Baseline not missing AND</td>
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<td>Baseline &lt; LLN (of Baseline)</td>
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11-May-2010  55
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Code</th>
<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
</tr>
</thead>
</table>
| Glucose, Serum Fasting    | GLUCF     | mg/dL | Low/High            | OR
|                           |           |       |                     | Value > 1.10 × ULN (of Value) when
|                           |           |       |                     | Baseline is missing OR
|                           |           |       |                     | LLN (of B) ≤ Baseline ≤ ULN (of B)                                                                                              |
|                           |           |       |                     | LOW if
|                           |           |       |                     | Value < 0.8 × Baseline when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline < LLN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value < LLN (of Value) when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline > ULN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value < 0.8 × LLN (of Value) when
|                           |           |       |                     | Baseline is missing OR
|                           |           |       |                     | LLN (of B) ≤ Baseline ≤ ULN (of B)                                                                                              |
|                           |           |       |                     | HIGH if
|                           |           |       |                     | Value > 2.0 × Baseline when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline > ULN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value > ULN (of Value) when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline < LLN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value > 1.5 × ULN (of Value) when
|                           |           |       |                     | Baseline is missing OR
|                           |           |       |                     | LLN (of B) ≤ Baseline ≤ ULN (of B)                                                                                              |
| Uric Acid                 | URIC      | mg/dL | High only           | Value > 2.0 × Baseline when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline > ULN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value > ULN (of Value) when
|                           |           |       |                     | Baseline not missing AND
|                           |           |       |                     | Baseline < LLN (of Baseline)                                                                                                     |
|                           |           |       |                     | OR
|                           |           |       |                     | Value > 1.5 × ULN (of Value) when
|                           |           |       |                     | Baseline is missing OR
|                           |           |       |                     | Baseline ≤ ULN (of Baseline)                                                                                                     |

**URINALYSIS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Code</th>
<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
</tr>
</thead>
</table>
| Glucose Urine             | UGLU      | N/A   | High only           | If Value >= 2 when Baseline = missing, or = 0 or = 0.5
|                           |           |       |                     | OR
|                           |           |       |                     | If Value >= 3 when Baseline = 1
|                           |           |       |                     | OR
|                           |           |       |                     | If Value >= 4 when Baseline ≥ 2                                                                                              |
| Protein, Urine            | UPRO      | N/A   | High only           | If Value >= 2 when Baseline = missing, or = 0 or = 0.5
|                           |           |       |                     | OR

11-May-2010
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Code</th>
<th>Units</th>
<th>Direction of Change</th>
<th>MA Criteria (applied to Value of labs collected on or after first dose only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood, Urine</td>
<td>UBLD</td>
<td>N/A</td>
<td>High only</td>
<td>If Value $\geq 3$ when Baseline $= 1$ OR If Value $\geq 4$ when Baseline $\geq 2$</td>
</tr>
<tr>
<td>Leukocyte Esterase, Urine</td>
<td>ULEUK</td>
<td>N/A</td>
<td>High only</td>
<td>If Value $\geq 2$ when Baseline $= \text{missing}$, or $= 0$ or $= 0.5$ OR If Value $\geq 3$ when Baseline $= 1$ OR If Value $\geq 4$ when Baseline $\geq 2$</td>
</tr>
<tr>
<td>RBC, Urine</td>
<td>URBC</td>
<td>hpf</td>
<td>High only</td>
<td>If Value $\geq 2$ when Baseline $= \text{missing}$, or $= 0$ or $= 0.5$ OR If Value $\geq 3$ when Baseline $= 1$ OR If Value $\geq 4$ when Baseline $\geq 2$</td>
</tr>
<tr>
<td>WBC, Urine</td>
<td>UWBC</td>
<td>hpf</td>
<td>High only</td>
<td>If Value $\geq 2$ when Baseline $= \text{missing}$, or $= 0$ or $= 0.5$ OR If Value $\geq 3$ when Baseline $= 1$ OR If Value $\geq 4$ when Baseline $\geq 2$</td>
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## APPENDIX 2  REGIONS AND COUNTRIES

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<thead>
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