# Apixaban versus warfarin for the management of post-operative atrial fibrillation: a prospective, controlled, randomized pilot study

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# Apixaban versus warfarin for the management of post-operative atrial fibrillation: a prospective, controlled, randomized pilot study

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# PROTOCOL SYNOPSIS

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|---|---|
| **Protocol Title:** | Apixaban versus warfarin for the management of post-operative atrial fibrillation: a prospective, controlled, randomized pilot study |
| **Site Numbers & Names:** | Sanford Medical Center, Fargo, ND |
| **Research Hypothesis:** | We hypothesize that there will be no significant differences between apixaban and warfarin anticoagulation strategies for the outcomes of venous thromboembolism/stroke or bleeding events when utilized for new-onset postoperative atrial fibrillation after isolated coronary artery bypass grafting (CABG). |
| **Study Schema:**<br>**Drugs / Doses / Length of Treatment)** | Patients who develop persistent atrial fibrillation after isolated coronary artery bypass grafting will be identified and randomized to anticoagulation with either warfarin (standard of care) or apixaban.<br>Warfarin will be dosed daily, with International Normalized Ratio (INR) monitoring per hospital protocol. After discharge, warfarin dosing will be managed by the anticoagulation clinic per protocol with a target INR of 2-3.<br>Apixaban will be dosed at 5 mg twice daily, or 2.5 mg twice daily in patients with at least two of the following characteristics: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum creatinine $\geq$ 1.5 mg/dL.<br>Patients will remain on anticoagulation until no longer needed (typically within 30 days of surgery). Study follow-up will be through the patient's 30-day follow-up appointment. |

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| **Study Objectives:** | 1) Primary endpoint: freedom from stroke or thromboembolic event will be captured.<br><br>2) Secondary endpoints:<br>-units of blood given after initiation of anticoagulation medication<br>-total post-operative length of stay<br>-duration from diagnosis of post-operative atrial fibrillation (POAF) to discharge from hospital<br>-time in therapeutic range of INR if on warfarin<br>-patient compliance percentage to apixaban if on apixaban<br><br>3) Safety assessments: major and minor bleeding events, as defined by the International Society on Thrombosis and Haemostasis, will be captured. Clinical events and blood product utilization will be identified and captured. |
| **Study Design:** | In this open-label, prospective, randomized pilot study, patients who develop atrial fibrillation after isolated coronary artery bypass grafting surgery will be identified. Patients with persistent atrial fibrillation (>12 hours) or recurrent sustained atrial fibrillation (≥2 episodes of atrial fibrillation lasting longer than 30 minutes) will be candidates for inclusion. Upon meeting study inclusion and exclusion criteria, and after informed consent, patients will be randomized to either the standard of care (warfarin per protocol) or apixaban arms of the trial. Routine postoperative care after CABG will occur in both groups. Upon discharge, anticoagulation in both groups will be managed by the anticoagulation clinic. Patients will be followed for 30 days after surgery. |
| **Accrual Goal:**<br>**(Total number of subjects)** | 56 patients |
| **Accrual Rate:**<br>**(Number of subjects expected per month)** | We anticipate enrolling 2-3 patients per month based on current projections. |
| **FPFV:**<br>**LPFV:**<br>**Follow Up:**<br>**(mm/dd/yy)** | FPFV: 9/1/16<br>LPFV: 12/31/18Follow up: 30 days per patient<br>Final Report: 3/31/19 |

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| **Correlative Studies:** **(PK/PD, etc.)** | Retrospective analysis conducted at our facility:<br><br>Anderson E, Johnke K, Leedahl D, Dyke,C. Novel oral anticoagulants vs warfarin for the management of postoperative atrial fibrillation: clinical outcomes and cost analysis. American Journal of Surgery. Volume 210, Issue 6,1095-1103[2] |
| **Inclusion Criteria:** | Patients diagnosed with new-onset persistent or recurrent atrial fibrillation after isolated CABG surgery. Persistent atrial fibrillation is defined as an episode of >12hours. Recurrent atrial fibrillation is defined as 2 or more episodes of atrial fibrillation lasting longer than 30 minutes. |

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| **Exclusion Criteria:** | 1. Patients undergoing valve replacement or with an artificial heart valve, or with moderate or severe mitral stenosis<br>2. Stroke within the previous 7 days.<br>3. Patients currently experiencing active bleeding precluding initialization of anticoagulation therapy in the opinion of their managing physician, or with increased bleeding risk (as determined by the attending surgeon) believed to be a contraindication to anticoagulation at the time of randomization.<br>4. Atrial fibrillation due to a reversible cause other than recent surgery<br>5. Planned major surgery requiring stoppage of anticoagulation therapy during the trial period.<br>6. Patients taking warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, or enoxaparin at home for any indication in the 15 days prior to surgery. Patients taking clopidogrel or ticagrelor within 5 days prior to surgery, patients taking prasugrel within 7 days prior to surgery, and patients taking ticlopidine within 10 days prior to surgery.<br>7. Patients receiving clopidogrel, ticagrelor, prasugrel, or ticlopidine during the study period.<br>8. Patients diagnosed with persistent atrial fibrillation chronically before undergoing surgery.<br>9. Patients with paroxysmal atrial fibrillation requiring oral anticoagulation prior to surgery.<br>10. Severe renal insufficiency (serum creatinine level of >2.5 mg/dL or CrCL<25 ml/min) for consecutive measurements.<br>11. Patients who are pregnant or of child-bearing age.<br>12. Patients <18 years of age.<br>13. Patients unable to give informed consent |

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| **Criteria for Evaluation:** **(Efficacy, safety, stopping rules, etc.)** | Efficacy will be measured by the freedom from systemic thromboembolism or stroke during the study period. Events relating to thromboembolism or stroke will be adjudicated using pre-determined definitions by independent committee members that remain blinded to the patient's treatment arm.<br>Safety, including major and minor bleeding will be quantified and defined by the Society on Thrombosis and Haemostasis, as described in section 6.4.2, subsection (2).<br>Clinical events that occur during the study period will be quantified and measured, including adverse events, serious adverse events, blood product utilization, length of stay, duration of atrial fibrillation, and time to adequate anticoagulation. |
| **Data Analysis Plan** | Efficacy and safety data will retrospectively assessed and analyzed after the patient has completed the 30-day course of therapy. Events relating to thromboembolism or stroke will be adjudicated using pre-defined endpoint definitions by independent committee members that remain blinded to treatment arm. Safety events, including major bleeding will be as defined by the International Society on Thrombosis and Haemostasis.[3] In the hospital, bleeding will be assessed daily by monitoring hemoglobin and the need for transfusions, and defined by a drop in hemoglobin of > 2 gm/dL in the previous 24 hours, or transfusion of at least two units of blood products. After discharge, we will monitor for readmissions related to bleeding, indicated by the need of transfusion of at least two units of blood products. |
| **Statistics:** | Continuous variables will be expressed as mean ± standard deviation or median with interquartile range (IQR) as appropriate. Continuous variables will be compared using t-tests for parametric data or Wilcoxon analysis for nonparametric data. We will complete the analysis in an intent-to-treat manner. We will include analysis for confidence intervals and other appropriate statistical tests to assess binary outcomes. We realize that statistical comparison between groups will be of limited utility in this pilot study as this study is not powered for comparison of events between groups. Data will be analyzed using JMP software, version 12.0.0 (Cary, NC). |

# 1 INTRODUCTION

Apixaban is a novel, orally active, potent, direct selective inhibitor of coagulation FXa that directly and reversibly binds to the active site of FXa and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. Apixaban is currently indicated to reduce stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of deep venous thrombosis (DVT), and for the prophylaxis of DVT in patients who have undergone hip or knee replacement surgery. Apixaban is not indicated for the treatment of atrial fibrillation caused by valvular heart disease or for patients with mechanical prosthetic valves requiring chronic oral anticoagulation.

Patients undergoing coronary artery bypass grafting (CABG) are at risk for the development of postoperative atrial fibrillation (POAF). POAF adversely impacts patient outcomes, and patients who develop POAF are at increased risk for stroke or thromboembolic complications, with an increased duration of hospitalization. Usually occurring in the early postoperative period and usually short-lived, POAF requires anticoagulation when persistent or recurrent. Duration of therapy for POAF is typically short-term, as POAF is usually short-term and self-limiting over 3-4 weeks.

Warfarin therapy has been the mainstay of therapy for patients with POAF. While the duration of therapy is usually short (3-4 weeks), complications of anticoagulation do occur. Additionally, warfarin therapy for POAF is associated with increased length of stay, need for monitoring, and bleeding complications.

Apixaban has been demonstrated to be superior to warfarin for the reduction of stroke or systemic embolism in patients with non-valvular atrial fibrillation. Additionally, major bleeding was significantly reduced in patients receiving apixaban compared to warfarin. The use of apixaban in patients with POAF has not been well studied, however, and whether these benefits will be seen in patients with POAF is unclear. In this small prospective pilot study, we aim to compare apixaban and warfarin anticoagulation strategies for the outcomes of venous thromboembolism/stroke and bleeding events when utilized in patients with new-onset postoperative atrial fibrillation after isolated coronary artery bypass grafting (CABG).

## 1.1 Scientific or Scholarly Background

Post-operative atrial fibrillation is defined as atrial fibrillation of new onset in the immediate post-operative period. Published rates of POAF after cardiac surgery is traditionally 20-30%, which is similar to rates observed at our facility.[1-4] Patients at the highest risk for POAF are those of advanced age; for each 10-year increase in age, the odds of developing atrial fibrillation after surgery increase by 75%.[5] Other patients at increased risk for developing POAF are those with a history of smoking, hypertension, or congestive heart failure, as well as patients undergoing urgent or emergent coronary artery bypass graft surgery. While atrial fibrillation occurs at any time after cardiac bypass surgery, it is most common within four days of surgery, and the peak incidence is on post-operative day two.[5] For persistent POAF, the American College of Cardiology, American Heart Association, and European Society of Cardiology recommend anticoagulation if rate-control measures and cardioversion therapy fail to return the patient to normal sinus rhythm.[6] In addition to warfarin, there are four novel anticoagulants approved for the management of non-valvular atrial fibrillation: apixaban, rivaroxaban, edoxaban, and dabigatran etexilate mesylate. Apixaban, rivaroxaban, and edoxaban are FDA approved for prophylaxis of cerebrovascular accidents and systemic thromboembolisms in the maintenance of atrial fibrillation.[7,8] Dabigatran is FDA approved for prophylaxis of thromboembolic disorders in patients with atrial fibrillation[9]. These novel agents have well-established safety and efficacy profiles, but have not been well studied for atrial fibrillation due to reversible causes such as POAF, or immediately after a major surgery such as a CABG. The ARISTOTLE study excluded patients with atrial fibrillation due to reversible causes such as surgery, and the RE-LY and ROCKET AF trials excluded patients with an increased risk of bleeding, including those that underwent major surgery in the previous 30 days, as well as patients with atrial fibrillation due to reversible causes, specifically cardiac surgery.[10-12]

## 1.2 Overall Risk/Benefit Assessment

Patients experiencing POAF after undergoing isolated CABG that require anticoagulation are currently placed on warfarin with a goal INR of 2-3. Compared to the current standard of care, apixaban may offer similar or improved safety and efficacy profiles, and this pilot study may provide a valuable signal of benefit and safety for apixaban use in the setting of POAF.

## 1.3 Research Hypothesis

In this pilot study, we hypothesize that there will be no significant differences between apixaban and warfarin anticoagulation strategies for the outcomes of venous thromboembolism/stroke or bleeding events, when utilized for new-onset postoperative atrial fibrillation after isolated coronary artery bypass grafting (CABG). This small prospective pilot study will not likely be adequately powered to show statistically significant differences in safety or efficacy between patients treated with apixaban or warfarin.

## 1.4 Study Rationale

Post-operative atrial fibrillation is defined as atrial fibrillation of new onset in the immediate post-operative period. Published rates of POAF after cardiac surgery is traditionally 20-30%, which is similar to rates observed at our facility.[2,4-6] Patients at the highest risk for POAF are those of advanced age; for each 10-year increase in age, the odds of developing atrial fibrillation after surgery increase by 75%.[7] Other patients at increased risk for developing POAF are those with a history of smoking, hypertension, or congestive heart failure, as well as patients undergoing urgent or emergent coronary artery bypass graft surgery. While atrial fibrillation occurs at any time after cardiac bypass surgery, it is most common within four days of surgery, and the peak incidence is on post-operative day two.[7] For persistent POAF, the American College of Cardiology, American Heart Association, and European Society of Cardiology recommend anticoagulation if rate-control measures and cardioversion therapy fail to return the patient to normal sinus rhythm.[8] In addition to warfarin, there are four novel anticoagulants approved for the management of non-valvular atrial fibrillation: apixaban, rivaroxaban, edoxaban, and dabigatran etexilate mesylate, although none of these have been studied in patients with POAF. Apixaban is indicated as follows:

**INDICATIONS AND USAGE----------**

ELIQUIS is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead topulmonary embolism (PE), in patients who have undergone hip or knee

replacement surgery. (1.2)

- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5).[1]

Rivaroxaban, and edoxaban are FDA approved for prophylaxis of DVT and prevention of pulmonary embolism and for the reduction of stroke and systemic thromboembolism in patients with nonvalvular atrial fibrillation.[9,10] Dabigatran is FDA approved for prophylaxis of thromboembolic disorders in patients with atrial fibrillation[11]. These novel agents have well-established safety and efficacy profiles, but have not been well studied for atrial fibrillation due to reversible causes such as POAF, or after major

surgery such as a CABG. The ARISTOTLE study excluded patients with atrial fibrillation due to reversible causes such as surgery, and the RE-LY and ROCKET AF trials excluded patients with an increased risk of bleeding, including those that underwent major surgery in the previous 30 days, as well as patients with atrial fibrillation due to reversible causes, specifically cardiac surgery.[12-14]

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

1) Efficacy: Venous thromboembolism or stroke, followed until postoperative day 30.

2) Safety: major and minor bleeding events, followed until postoperative day 30, as defined by the International Society on Thrombosis and Haemostasis[3]

3) Clinical relevant non-major bleed.

4) Transfusions: units of blood or blood products given after the first dose of anticoagulation.

5) Total post-operative length of stay in days, defined as the time the patient leaves the operating room (day 0) until hospital discharge. Length of say will increase by 1 day with each midnight that is passed.

6) Time in therapeutic range of INR, if on warfarin, (eg. 2-3), measured as a percentage and defined for each patient using the Rosendaal equation.

7) Patient compliance percentage to apixaban dosing, calculated as a percentage using the following equation

a. (# doses prescribed - # of doses not taken and returned to investigator at follow up appointment) / # doses prescribed; the follow up visit will occur after anticoagulation prescription has ended.

# 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 Harmonisation (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, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (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 tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment).

## 3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, 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 should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## 3.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Investigators must:

**1)** Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

**2)** Allow time necessary for subject to inquire about the details of the study.

**3)** Obtain an informed consent signed and personally dated by the subject and by the person who conducted the informed consent discussion.

**4)** Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

**5)** Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject 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.

**6)** Reconsenting of patients can be done in person or, if the patient is unable to reconsent in person, over the phone. If the reconsent is required to be performed over the phone, the coordinator will send an updated consent form to the patient via mail or electronically. When the patient has received the consent, the coordinator will review the consent with the patient over the phone. Any questions can be answered by the coordinator during the consenting process. The patient will then send the original signed consent back to the coordinator. The coordinator who conducted the phone consent will sign and date the applicable line and upload to the patient's chart. The coordinator must also document the consent discussion and receipt of the consent in the patient's EMR.

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

# 4 INVESTIGATIONAL PLAN

## 4.1 Study Design and Duration

Planned study design: prospective, controlled, randomized pilot study

Screening procedures/study population: Patients will be eligible for screening if they develop atrial fibrillation in the postoperative period that:

1. Persists 12 hours or more.
2. Develop recurrent atrial fibrillation with two or more episodes of persistent AFib of at least 30 minutes duration during the same hospital stay.

Number of subjects per arm: 28

Randomization ratio/method: 1:1, determined in permuted block fashion

Duration of treatment: 30 days of oral anticoagulation therapy. This period will start with the first dose of anticoagulation (either apixaban or warfarin) given in the hospital, and continue until the patient's 30-day post-operative appointment.

Criteria for evaluation:

- Efficacy: systemic thromboembolism or stroke will be assessed retrospectively after the patient has completed the 30-day course of therapy.
    - Events relating to thromboembolism or stroke will be adjudicated using pre-determined definitions by independent committee members that remain blinded to the patient's treatment arm.
- Safety: major bleeding will be as defined by the Society on Thrombosis and Haemostasis, as follows:
    - 1. Fatal bleeding, and/or
    - 2. Symptomatic bleeding that occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or
    - 3. Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L (2g/dL) or more, or leading to transfusion of two or more units of whole blood or red cells within 24-48 hours of the bleeding and/or
    - 4. Surgical site bleeding that requires a second intervention – open, arthroscopic, endovascular- or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or
    - 5. Unexpected surgical site bleeding, prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon, with a fall in hemoglobin of at least 20 g/L (2g/dL) or transfusion of two or more units of whole blood or red cells within 24 hours of the bleeding. [3]

In the hospital, bleeding will be assessed daily by monitoring hemoglobin and the need for transfusions. After discharge and until the patient's 30-day post-operative evaluation, we will monitor for readmissions related to bleeding, indicated by the need for transfusion of at least two units of blood products. Any patient phone calls that already occur as part of routine post-operative care will continue; however, there are no additional post-discharge phone calls to the patient related to this study.

## 4.2 Study Population

### 4.2.1 Inclusion Criteria

**1) Signed Written Informed Consent**

- Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel. This informed consent will be scanned into the patient's EMR, as well as retained for a period not less than three years after the completion of the study.

**2) Target Population**

- Patients diagnosed with new-onset persistent or recurrent atrial fibrillation after isolated CABG surgery. Persistent atrial fibrillation is defined as an episode of >12 hours. Recurrent atrial fibrillation is defined as two or more episodes of atrial fibrillation lasting longer than 30 minutes.

**3) Age and Reproductive Status**

- Males and Females, at least 18 years of age
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug. Patients undergoing isolated CABG must have this tested and documented prior to the procedure, and this will be verified prior to randomization.
- Women must not be breastfeeding.
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s): 30 days of treatment plus 5 half-lives of study drug Apixaban (3 days) or warfarin (8 days) plus 30 days (duration of ovulatory cycle) for a total of 38 days post-treatment completion.
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s): 30

days of treatment plus 5 half-lives of study drug Apixaban (3 days) or warfarin (8 days) plus 90 days (duration of sperm turnover) for a total of 98 days post-treatment completion.

- Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partnerFemale partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

### 4.2.2 Exclusion Criteria

**Target Disease Exceptions**

- Atrial fibrillation due to a reversible cause other than recent surgery
- Patients diagnosed with persistent or paroxysmal atrial fibrillation chronically before undergoing surgery

- Patients with mechanical heart valves

**Medical History and Concurrent Diseases**

- Patients currently experiencing active bleeding precluding initialization of anticoagulation therapy in the opinion of their managing physician, or with increased bleeding risk (as determined by the attending surgeon) believed to be a contraindication to anticoagulation at the time of randomization Planned major surgery requiring stoppage of anticoagulation therapy during trial period
- Stroke within the previous 7 days
- Moderate or severe mitral stenosis
- Conditions other than atrial fibrillation that required anticoagulation (prosthetic mechanical heart valve)

**Concomitant Medications**

- 
- Patients taking warfarin, apixaban, rivaroxaban, dabigatran, edoxaban, or enoxaparin at home for any indication in the 15 days prior to surgery. Patients taking clopidogrel or ticagrelor within 5 days prior to surgery, patients taking prasugrel within 7 days prior to surgery, and patients taking ticlopidine within 10 days prior to surgery
- Patients receiving clopidogrel, ticagrelor, prasugrel, or ticlopidine during the study period

**Physical and Laboratory Test Findings**

- Severe renal insufficiency (serum creatinine level of >2.5 mg/dL or CrCL<25 ml/min) for consecutive measurements

**Allergies and Adverse Drug Reactions**

- Allergies to warfarin or apixaban, or components of warfarin or apixaban

**Sex and Reproductive Status**

- ***See Section on WOCBP above (Section 4.2.1, item # 3.)***

**Other Exclusion Criteria**

- Prisoners or subjects who are involuntarily incarcerated.
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Patients <18 years of age.
- Patients unable to give informed consent.

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 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal :

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

### 4.2.4 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, 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.
- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant.

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- While patients may request withdrawal from the study at any time, they will be advised to check with their medical provider before discontinuing any anticoagulant medication, for their safety.
- Subjects can voluntarily withdraw from the study at any time, but the investigators will continue to follow the patient so that an intent-to-treat analysis can be performed. Failure to take study medication as prescribed, or failure to follow up as directed with the anticoagulation clinic, will be noted in our analysis to the best extent we are able.
- Any data collected before withdrawal will be used for study outcomes, although it will be noted that the participant did not complete the 30-day course of therapy. Attempts will be made to determine and note the reason for withdrawal.
- All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in Section 6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

# 5 TREATMENTS

## 5.1 Study Treatment: Apixaban

**Definition of Investigational Product:** 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 marketing 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, the investigational product is apixaban. The control (current standard of care) is warfarin.

**Definition of Non-Investigational Product:** Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. In this protocol, the non-investigational products are: none.

### 5.1.1 Identification

| Product Description / Class and Dosage Form | Potency | Blinded or Open Label | Packaging/ Appearance |
|---|---|---|---|
| Apixaban | 5mg | Open | Pink, oval, biconvex<br>Debossed with "894" on one side and "5" on the other side |
| Apixaban | 2.5mg | Open | Yellow, round, biconvex<br>Debossed with "893" on one side and "2½" on the other side |
| Warfarin | 1mg 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7.5mg, 10mg | Open | All strengths are tablets.<br>1mg: pink, 2mg: lavender,<br>2.5mg: light green, 3mg: tan,<br>4mg: blue, 5mg: peach,<br>6mg: teal, 7.5mg: yellow,<br>10mg: white |

Medication storage:

Apixaban: Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F). Protect from light and moisture.

Warfarin: Store at controlled room temperature, (59°-86°F, 15°-30°C). Protect from light and moisture.

### 5.1.2 Handling and Dispensing

The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

### 5.1.3 Drug Destruction

Ensure that arrangements have been made for investigational drug disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures.

## 5.2 Drug Ordering and Accountability

### 5.2.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of STUDY DRUG (apixaban) may be ordered through the BMS protocol manager by completing a Drug Request Form. The first request will take place upon site opening.

### 5.2.2 Re-Supply

Drug re-supply request form should be submitted electronically or by fax to the BMS protocol manager at least ten business days before the expected delivery date.

### 5.2.3 Accountability

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

## 5.3 Method of Assigning Subjects to a Treatment

Patients will be randomized to a treatment arm (apixaban or warfarin) in a 1:1 ratio by utilizing a random permuted block method, using blocks of four to eight, which was randomly generated. This ensures that with every four, six, or eight patients randomized, an equal number of subjects will be in each treatment arm, without the possibility of study personnel knowing or predicting the next randomization event.

## 5.4 Selection and Timing of Dose for Each Subject

**Apixaban**: Apixaban is to be dosed at 5 mg by mouth twice daily, except in the case of the criteria listed below in "dose modifications". The duration of therapy will be at least 30 days. The patient's physician may determine that anticoagulation therapy should be continued after the study period, based on their examination of the patient at the 30-day post-operative examination.

Apixaban should not be used if a patient has active pathological bleeding.

If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with twice daily administration as before. The dose should not be doubled to make up for a missed dose.

Apixaban can be taken with or without food.

Apixaban is not recommended in patients with severe hepatic impairment. No dose adjustment is recommended for patients with renal impairment alone, including those with end-stage renal disease (ESRD) maintained on hemodialysis, except nonvalvular atrial fibrillation patients who meet the criteria for dosage adjustment. Patients with ESRD (CrCl <15 mL/min) receiving or not receiving hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis.

**Warfarin:** While patients are hospitalized, warfarin will be dosed daily, with daily INR monitoring per hospital protocol. Daily doses may vary from 0.5mg to 15mg by mouth, as determined by patient specific factors such as patient size, hepatic function, INR, concomitant medications, diet, or other factors. Based on these factors or others not listed, there may also be days in which the patient is prescribed to not get does not receive a dose of warfarin.

After discharge from the hospital, warfarin dosing will be subsequently managed by an anticoagulation clinic, per established protocols. All patients will have a goal INR of 2-3 during the duration of the study. The duration of therapy will be at least 30 days. The patient's physician may determine that anticoagulation therapy should be continued after the study period, based on their examination of the patient at the 30-day post-operative examination.

Warfarin should not be used if a patient has active pathological bleeding.

If a dose of warfarin is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with daily administration as before, or as recommended by the anticoagulation clinic. The dose should not be doubled to make up for a missed dose.

Warfarin can be taken with or without food, but it is recommended to maintain a consistent intake of vitamin K containing foods.

### 5.4.1 Dose Modifications

Apixaban: in patients with at least 2 of the following characteristics, age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L), the recommended dose of apixaban is 2.5 mg twice daily.

Warfarin: doses of warfarin will be determined on a daily basis while the patient is in the hospital. After discharge from the hospital, after each INR check, a pharmacist or nurse will contact the patient to communicate the appropriate dosing.

### 5.4.2 Temporary Discontinuation of Apixaban or Warfarin

Discontinuing anticoagulants, including apixaban or warfarin, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided, and if anticoagulation with apixaban and warfarin must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

## 5.5 Blinding/Unblinding

Not applicable; study is unblinded.

## 5.6 Concomitant Treatments

### 5.6.1 Prohibited and/or Restricted Treatments

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include

aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs).

### 5.6.2 Other Restrictions and Precautions

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping apixaban and prior to the intervention is not generally required. Apixaban should be restarted after the surgical or other procedures as soon as adequate hemostasis

has been established. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

The concomitant use of apixaban or warfarin with antiplatelet agents increases the risk of bleeding. In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban. Patients taking clopidogrel or ticagrelor within 5 days prior to surgery, patients taking prasugrel within 7 days prior to surgery, and patients taking ticlopidine within 10 days prior to surgery, and patients taking clopidogrel, ticagrelor, prasugrel, or ticlopidine during the study period will be excluded from participation in this study.

Use apixaban and warfarin with caution when co-administered with non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.

### 5.7 Treatment Compliance

Patient compliance will be monitored during the study. While the patient is hospitalized, we will monitor whether apixaban or warfarin is given as directed by the study coordinator. After the patient has been discharged from the hospital, apixaban compliance will be measured by asking the patient to bring any unused medication to their 30-day post-operative appointment, where remaining tablets will be counted. As 60 tablets will be dispensed to each patient (30-day supply), we use the following formula:

[(60-(# of remaining tablets)) * 100)] / [2 * (days since filled)] = percent compliance.

After hospital discharge, warfarin compliance will be monitored by measuring the time in therapeutic INR range (2-3).

## 6 STUDY ASSESSMENTS AND PROCEDURES

### 6.1 Time and Events Schedule

If a subject chooses to be removed from the study, withdraws informed consent, or if therapy must be stopped in the interest of the patient's safety, data collected to that point of the study will be collected for intent-to treat analysis. We will document the reason for a patient's early withdrawal from the study, or the discontinuation of treatment for a patient by the patient's physician or study coordinator.

After the 30-day post-operative physician examination, there will no further patient assessments. Analysis of all outcomes will be done by EMR analysis, except for treatment compliance as noted above.

## Time and Events Schedule for Protocol: CV185-505

| Procedure | Prior to Surgery (day of surgery, or <30 days prior) | After Diagnosis of AFib | Upon Hospital Discharge | At Each Anticoagulation Clinic Visit (warfarin) | At 30-Day Post-Operative Examination | After 30-Day Post-Operative Examination |
|---|---|---|---|---|---|---|
| **Eligibility Assessments** | | | | | | |
| Informed Consent | | X | | | | |
| Medical History | | X | | | | |
| Inclusion/Exclusion Criteria | | X | | | | |
| **Clinical Drug Supplies** | | | | | | |
| Randomize | | X | | | | |
| Dispense Study Treatment | | | X | | | |
| Patient Medication Consultation | | | X | | | |
| **Safety Assessments** | | | | | | |
| Pregnancy Test for WOCBP | X | | | | | |
| Renal Function Test | X | X | | | | |
| Hepatic Function Test | | X | | | | |
| INR measurement | X | X | | X | | |
| Monitoring for Bleeding Events | | | X | X | X | |
| Monitoring for Thrombotic Events | | | X | X | X | |
| **Efficacy Assessments** | | | | | | |
| Measure Apixaban Adherence | | | | | X | |
| EMR Analysis of All Other Outcomes | | | | | | X |
| Outcomes Statistical Analysis | | | | | | X |

## 6.2 Study Materials

Bristol-Myers Squibb (BMS) will provide apixaban at no cost for this study.

## 6.3 Safety Assessments

1) Major bleeding, as defined by the International Society on Thrombosis and Haemostasis based on the following criterion:

a. Fatal bleeding, and/or

b. Symptomatic bleeding that occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or

c. Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L (2g/dL) or more, or leading to transfusion of two or more units of whole blood or red cells within 24-48 hours of the bleeding and/or

d. Surgical site bleeding that requires a second intervention – open, arthroscopic, endovascular- or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or

e. Unexpected surgical site bleeding, prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon, with a fall in hemoglobin of at least 20 g/L (2g/dL) or transfusion of two or more units of whole blood or red cells within 24 hours of the bleeding. [3]

2) Clinical relevant non-major bleed, defined as any notable bleeding not classified as major.

3) Pregnancy tests will be performed pre-operatively on the day of surgery for all WOCBP, via urine hCG screening.

4) A baseline renal function panel will be obtained either pre-operatively or within 30 days of surgery. The renal function panel includes: glucose, BUN, creatinine, BUN/creatinine ratio, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, albumin, and anion gap.

5) The hepatic function test panel will be ordered before initiating warfarin (if a recent baseline is not available). This panel includes: total protein, albumin, alk phos, AST, ALT, total bilirubin, direct bilirubin, and indirect bilirubin.

6) INR will be checked before surgery to ensure the patient's INR is within normal limits in preparation for their surgery, regardless of whether they were previously on warfarin, and again upon initiation of warfarin therapy. INR will be checked daily in the hospital, and at each visit to the anticoagulation clinic. These visits are usually scheduled within three days of discharge from the hospital, then twice weekly until the INR is therapeutic, then weekly for the duration of the study.

## 6.4 Study Assessments

### 6.4.1 Primary Assessment

The primary assessment is freedom from systemic thromboembolism or stroke: this will be as diagnosed by a physician, to include pulmonary embolism, deep vein thrombosis, and both hemorrhagic and ischemic stroke. Events relating to thromboembolism or stroke will be adjudicated using pre-determined definitions by independent committee members that remain blinded to the patient's treatment arm.

### 6.4.2 Secondary Assessments

1) Units of blood or blood products given after the first dose of anticoagulation.

2) Total post-operative length of stay: This will be measured from the date/time of the end of the subject's surgery until the date/time of the patient's discharge from the hospital. This will be measured in hours, to the nearest tenth of an hour.

3) Duration from diagnosis of post-operative atrial fibrillation (POAF) to discharge from the hospital: This will be measured from the time of the EKG that is obtained after AFib is noted on telemetry (confirming the diagnosis of AFib), until hospital discharge. This will be measured in hours, to the nearest tenth of an hour.

4) Time in therapeutic range of INR, if on warfarin, (eg. 2-3), measured as a percentage and defined for each patient using the Rosendaal equation

5) Patient compliance percentage to apixaban: measured by asking the patient to bring any unused medication to their 30-day post-operative appointment, where remaining tablets will be counted. This will be calculated as a percentage using the following

equation: (# doses prescribed - # of doses not taken and returned to investigator at follow up appointment) / # days prescribed.

# 7 ADVERSE EVENTS

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient 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.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term “reasonable causal relationship” means there is evidence to suggest a causal relationship.

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 adverse events).

## 7.1 Serious Adverse Events

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

- 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
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on 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 above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

***NOTE:** The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
-

**Adverse Events of Special Interest**

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

### 7.1.1 Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, 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 Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the FDA MedWatch Form 3500A ; Pregnancies on a Pregnancy Surveillance Form.

**SAE Email Address:** Worldwide.Safety@BMS.com

**SAE Fax Number:** 609-818-3804

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.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

### 7.1.2 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR). The investigator will request a safety data reconciliation report to aepbusinessprocess@bms.com. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

### 7.1.3 Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, provide details of the following:

- Any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.
- BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH

5600 Fishers Lane

Rockville, MD 20852-9787

Fax: 1-800-FDA-0178 (1-800-332-0178)

http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology

Bristol-Myers Squibb Company

Fax Number: 609-818-3804

Email: Worldwide.safety@bms.com

## 7.2 Non-Serious Events

A non-serious adverse event is an AE not classified as serious.

### 7.2.1 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Non-serious adverse event 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.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Non-serious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

## 7.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, use the term anemia rather than low hemoglobin value).

Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

## 7.4 Pregnancy

If, following initiation of the 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 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

## 7.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

### 7.6 Other Safety Considerations

Any significant worsening 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 as a non-serious or serious adverse event, as appropriate, and reported accordingly.

## 8 DATA MONITORING COMMITTEE

Not Applicable.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 Sample Size Determination

For this pilot study, we anticipate 300 patients will be eligible for inclusion over the 28-month study period (estimate two patient enrollments per month). With an expected POAF rate of 25%, and a 5% exclusion rate, we expect 70 patients will be eligible for study participation within the study period. We will enroll the first 56 patients meeting the required criteria, to be included in the final analysis of endpoints. This pilot study should therefore be used as a reference for future studies of novel anticoagulants use in patients that have had a recent surgery, or have atrial fibrillation due to other reversible causes.

### 9.2 Populations for Analyses

Patients diagnosed with post-operative atrial fibrillation after undergoing isolated CABG that require anticoagulation and meet inclusion/exclusion criteria will be asked to participate in this study.

### 9.3 Analyses

Continuous variables will be expressed as mean ± standard deviation or median with interquartile range (IQR) as appropriate. Continuous variables will be compared using t-

tests for parametric data or Wilcoxon analysis for nonparametric data. We will complete the analysis in an intent-to-treat manner. We will include analysis for confidence intervals and other appropriate statistical tests to assess binary outcomes. We realize that statistical tests alone will be of limited value as this is a pilot study. Data will be analyzed using JMP software, version 12.0.0 (Cary, NC). All statistics collected will be analyzed after completion of the 30-day trial period for all subjects.

# 10 STUDY MANAGEMENT

## 10.1 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, 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.

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.

Patients who need to be reconsented can be reconsented over the phone if they are unable to do so at the clinic. The coordinator will send an updated consent form to the patient via mail or electronically. When the patient has the consent, the coordinator will review the consent with the patient over the phone. Any questions can be answered by the coordinator during the consenting process. The patient will then send the original signed

consent back to the coordinator. The coordinator who conducted the phone consent will sign and date the applicable line and upload to the patient's chart. The coordinator must also document the consent discussion and receipt of the consent in the patient's EMR.

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

***For complete information on the requirements for protocols, protocol amendments, and informed consents, refer to 21CFR50.***

## 10.2 Records Retention

### 10.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

### 10.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the BMS) is maintained at each study site where study drug and noninvestigational product(s) is/are inventoried and dispensed. 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
- 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 (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

## 10.3 Destruction of Investigational Product

If the study drugs are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

# 11 GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Adverse Reaction | An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product |
| Expedited Safety Report | Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures. |
| SUSAR | Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC). |
| Unexpected Adverse Reaction | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product) |

# 12 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AFib | Atrial Fibrillation |
| BMS | Bristol-Myers Squibb |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DVT | Deep Vein Thrombosis |
| EMR | Electronic Medical Record |
| ESR | Expedited Safety Report |
| ESRD | End Stage Renal Disease |
| FDA | Food and Drug Administration |
| FSH | Follicle-Stimulating Hormone |
| GCP | Good Clinical Practice |
| HCG | Human Chorionic Gonadotropin |
| HRT | Hormone Replacement Therapy |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug (Application) |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| ISR | Investigator-Sponsored Research |
| NCI | National Cancer Institute |
| NSAE | Non-Serious Adverse Event |
| PE | Pulmonary Embolism |
| SAE | Serious Adverse Event |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| WOCBP | Women of Child-Bearing Potential |

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