



**A PHASE IV TRIAL TO ASSESS THE EFFECTIVENESS OF APIXABAN  
COMPARED WITH USUAL CARE ANTICOAGULATION IN SUBJECTS WITH  
NON-VALVULAR ATRIAL FIBRILLATION UNDERGOING CARDIOVERSION**

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**Document History**

<b>Document</b>	<b>Version Date</b>	<b>Summary of Changes and Rationale</b>
Original protocol	19-Mar-2014	Not Applicable
Amendment 1	30-Jul-2014	Following Japan Regulatory Authority (PMDA) advice, for Japan only, the optional Apixaban loading dose has been removed & the inclusion criterion for age increased to 20 years for those subjects participating in this study in Japan only.
Amendment 2	16-Feb-2015	Modification of the Exclusion Criterion #1 to allow a limited period of treatment with an oral anticoagulant prior to study entry. Additional exclusion criterion added/edited for safety and clarity. Minor administrative clarifications and template up-dates.
Amendment 3	22-Feb-2016	<p>Main reason for amendment:</p> <p>Sections 4.2 and 5.2.3.2: Request from regulatory authorities to incorporate the Protocol Administrative Changes and Clarifications letter (dated 08-Jul-2015) pertaining to sections 4.2 exclusion criteria #6 and 5.2.3.2 into a substantial protocol amendment.</p> <p>Other changes:</p> <p>Schedule of Activities: added footnote referring to Figure 2 for examples of timing of Visit 3.</p> <p>Section 3: Added Figure 2 (Examples of timing for Visit 3).</p> <p>Section 4.1 criteria #1: Added that atrial fibrillation must be documented by electrocardiogram (ECG) and that subjects presenting with atrial flutter with no evidence of atrial fibrillation are not eligible for enrolment.</p> <p>Section 4.1 criteria #2: Corrected age range for Korea.</p> <p>Sections 5.2.2; 6.1.2; 6.2: Incorporating the Protocol Administrative Change Letter (dated 25-Nov-2015) clarifying the requirement for visual inspection for subjects randomized to usual care.</p>

		<p>Section 5.2.3: Added details of apixaban dosing period for subject who have spontaneously reverted to normal sinus rhythm before cardioversion</p> <p>Section 5.2.3.2: Incorporation of Protocol Deviation Alert Letter dated 10-Jun-2015 prohibiting co-administration of parenteral heparin and apixaban.</p> <p>Section 5.2.3.2: Clarified that INR values will be recorded in the CRF.</p> <p>Section 5.2.3.2: Rearranged wording pertaining to Japan specific requirement.</p> <p>Section 5.2.4: Clarified compliance requirements.</p> <p>Section 5.4: Added that the co-administration of parenteral heparin and apixaban is prohibited.</p> <p>Section 6.1.1: Clarified timing of ECG taken at Visit 1.</p> <p>Section 6.1.2: Added referral to section 5.2.2.</p> <p>Section 6.2: Added referral to section 5.2.2.</p> <p>Section 6.3: Referral to Figure 2 for examples of timing of Visit 3.</p> <p>Section 7.2: Clarified timing of ECG taken at Visit 1.</p> <p>Section 8: Updated throughout with required BMS safety language.</p> <p>Section 15.1: Updated Communication of Results by Pfizer/BMS.</p> <p>Minor formatting corrections have been applied throughout the protocol.</p>
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

## **PROTOCOL SUMMARY**

**Background and Rationale;** Cardioversion (electrical or pharmacological) is an effective method of converting atrial fibrillation (AF) to sinus rhythm and should be considered as early as possible in order to initiate a long-term rhythm control management strategy for patients, and avoid irreversible atrial re-modeling.

In a sub-group analysis of ARISTOTLE trial data, 743 cardioversions were performed in 540 subjects, and the effectiveness of apixaban was demonstrated in the 30 days following cardioversion. However, in this study subjects who underwent cardioversion had already been chronically anticoagulated either prior to entry or, if treatment-naïve, as part of the trial. Thus, there was no information on the effectiveness of apixaban in subjects newly presenting with AF who were anticoagulant-naïve and in whom an early cardioversion was indicated, eg, with or without an image-guided approach. This study is being conducted to assess the effectiveness of apixaban compared with usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants)) in subjects with non-valvular AF indicated for early cardioversion and initiation of anti-coagulation in a real world clinical practice setting.

**Objectives and Endpoints;** The study objective is to assess the occurrence of clinical endpoints in non-valvular AF subjects (ie, without rheumatic mitral valve disease, a prosthetic heart valve, or valve repair) indicated for early cardioversion and treated with apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants)). Clinical endpoints include: occurrence of stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding, and death. Additional information on the cardioversion details (timing, type, attempts, and rhythm status), length of in-hospital stay and use of image guidance will also be collected.

**Study Design;** This is a randomized, active controlled, parallel-group, open label study. Approximately 1500 subjects will be randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants)). Following randomization, endpoints will be collected during the 30 days following the cardioversion or during the 90 days post randomization if cardioversion is not performed within that time frame.

**Study Treatments;** Apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants)) will be administered from randomization up to 30 days following cardioversion or 90 days post randomization if cardioversion is not performed.

**Statistical Methods;** Baseline demographics, endpoints, adverse events and serious adverse events (SAEs) will be reported by randomized treatment. Number of observations and proportions will be given for categorical or binary variables, number of observations, mean, standard deviation, median minimum and maximum will be given for continuous variables; time-to-event data will be displayed using Kaplan-Meier techniques; hazard ratio will be calculated.

**SCHEDULE OF ACTIVITIES**

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to [Study Procedures](#) and [Assessments](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Procedure	Visit 1 Enrollment Screening/Randomization <sup>a</sup>	Visit 2 Cardioversion (or planned cardioversion)	Visit 3 Follow-Up (30 days post cardioversion (Visit 2) or up to 90 days following Visit 1) <sup>e</sup>
Visit Windows			±7 days
Informed Consent	X		
Obtain Alternative Contact	X		
Inclusion/Exclusion	X		
Demographics	X		
Medical History	X		
CHA <sub>2</sub> DS <sub>2</sub> -VASc score <sup>b</sup>	X		
Local Laboratory Parameters	X	X	X
Electrocardiogram	X (may be obtained on the day prior to Visit 1)	X	X
Randomization	X		
Cardioversion <sup>c</sup>		X	
Endpoint Assessments <sup>d</sup>		X	X
Dispense Study Drug	X	X	
Collect Study Drug		X	X
Study Drug Compliance Check		X	X
Adverse Event Assessment		X	X

a. Screening/Randomization could occur on the same day

b. CHA<sub>2</sub>DS<sub>2</sub>-VASc - Congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex category risk score

c. Cardioversion details (timing, type, attempts, and rhythm status) and use of image guidance

d. Endpoints; stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding, and all cause death

e. See Figure 2 for examples of timing of Visit 3.

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## 1. INTRODUCTION

Apixaban is a novel, orally active, selective inhibitor of the coagulation factor Xa (FXa) developed by Bristol-Myers Squibb (BMS) and Pfizer as an anticoagulant and antithrombotic agent. Apixaban is a reversible and highly potent inhibitor of human FXa with a high degree of selectivity over other coagulation proteases and structurally related enzymes involved in digestion and fibrinolysis.

### 1.1. Indication

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

### 1.2. Background and Rationale

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accounting for approximately one third of hospitalizations attributed to cardiac rhythm disturbances, and the life time risk of developing AF is 1 in 4 for adults 40 years of age or older.<sup>1,2</sup> Cardioversion (electrical or pharmacological) is an effective method of converting AF to sinus rhythm and should be considered as early as possible in order to initiate a long-term rhythm control management strategy for subjects, and avoid irreversible atrial re-modeling.

Electrical cardioversion in patients with AF is associated with an increased risk for thromboembolic events, which might exceed 5% with inadequate or no oral anticoagulation.<sup>3,4</sup> Therapeutic oral anticoagulation with a vitamin K antagonist (eg, warfarin) will reduce the risk of thromboembolic events during and after cardioversion to less than 1%.<sup>5-7</sup> Current AF guidelines recommend therapeutic anticoagulation for at least 3 weeks before and at least 4 weeks after cardioversion for patients with AF of more than 48 hours duration or with unknown duration.<sup>8,9</sup> The guidelines also recommend an abbreviated anticoagulation strategy with an image guided approach (eg, transesophageal echocardiography (TEE/TOE) or computed tomographic (CT) scan).

The ACUTE study,<sup>6</sup> a multicentre, randomized prospective study, compared a TEE-guided strategy of abbreviated therapeutic anticoagulation with intravenous unfractionated heparin (UFH) (started 24 h before cardioversion) or conventional warfarin (International Normalized Ratio (INR) 2.0-3.0, at least 3 weeks before cardioversion) strategy in 1222 patients with AF of more than 2 days duration planned for electrical cardioversion. There was no significant difference between the two treatment groups in the rate of embolic events within the eight-week study period; however, the rate of hemorrhagic events was significantly lower in the TEE group (18 events [2.9 percent] vs. 33 events [5.5 percent], probability (p) =0.03). Patients in the TEE group also had a shorter time to cardioversion (mean [±standard deviation (SD)], 3.0±5.6 vs. 30.6±10.6 days). The authors conclude that the strategy of using TEE to guide treatment may be considered a safe and clinically effective alternative to the conventional treatment strategy.

The efficacy and safety of apixaban for the prevention of stroke and systemic embolism in AF patients was demonstrated in 2 randomized, double-blind, Phase 3 trials: ARISTOTLE (apixaban vs. warfarin; n = 18,201) in patients suitable for Vitamin K antagonist (VKA)

therapy<sup>10</sup> and AVERROES (apixaban vs. aspirin; n = 5599) in patients unsuitable for VKA therapy.<sup>11</sup> Both studies were conducted in patients with non-valvular (ie, without rheumatic mitral valve disease, a prosthetic heart valve, or valve repair), persistent, paroxysmal, or permanent AF or atrial flutter, and 1 or more additional risk factors.

In the ARISTOTLE trial, the rate of the primary outcome (ischemic or hemorrhagic stroke or systemic embolism) was 1.27% per year in the apixaban group, compared with 1.60% per year in the warfarin group (Hazard Ratio (HR) = 0.79; p<0.001 for non-inferiority; p = 0.01 for superiority)<sup>10</sup> The rates of major or clinically relevant non-major bleeding events was also reduced by apixaban compared to warfarin, 4.07 %/ year vs. 6.01 %/year, p<0.001.

The AVERROES trial demonstrated a clear efficacy benefit in favor of apixaban and an independent Data and Safety Monitoring Board recommended early termination after 1.1 years of mean study participation. The rate of primary outcome events (stroke or systemic embolism) in patients assigned to apixaban was 1.6% per year, compared to 3.7% per year among those assigned to aspirin (HR = 0.45; p<0.001).<sup>12</sup>

Apixaban (Eliquis™) has regulatory approval for prevention of stroke and systemic embolism in patients with non-valvular AF since November 2012 in the European Union (EU) and since December 2012 in Canada, Japan and the US.

Apixaban also has marketing authorization in the EU for prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery since 2011.

In a sub-group analysis of ARISTOTLE data, where 743 cardioversions were performed in 540 subjects, the effectiveness of apixaban was demonstrated in the 30 days following cardioversion, with no stroke or systemic embolism events in either group, 1 and 1 major bleeds, and 2 and 2 deaths in the apixaban and warfarin groups, respectively.<sup>13</sup>

However, in this ARISTOTLE sub-group analysis, subjects who underwent cardioversion had already been chronically anticoagulated either prior to entry or, if treatment-naïve, as part of the trial. Thus, there was no information on the effectiveness of apixaban in subjects newly presenting with AF who were anticoagulant-naïve and in whom an early cardioversion was indicated, eg, with an image-guided approach or a definite onset of symptoms ≤48 hours. An image-guided approach facilitates cardioversion earlier than the conventional minimum of 3 weeks of anticoagulation that would normally be required prior to cardioversion. It is expected that most image-guided cardioversions would occur from a few hours to a few days after initial presentation. In subjects with a clearly defined onset of symptoms ≤48 hours, guidelines suggest that cardioversion may be performed early without image-guidance.<sup>8,9</sup>

Therefore, this study is being conducted to assess the effectiveness of apixaban compared with usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants (NOACs)) in subjects with non-valvular AF indicated for early cardioversion and initiation of anticoagulation in a real-world, clinical practice setting. The image guidance approach in subjects with >48 hours or unknown duration and non-guided with symptoms ≤48 hours will be referred to as “early

cardioversion” throughout this protocol. Subjects with symptom onset >48 hours or unknown duration and not following an image guided approach are expected to receive the conventional anticoagulation strategy (minimum of 3 weeks prior to cardioversion) as per guidelines.

The overriding design principle of this study is that of a randomized observational approach, sometimes known as a ‘pragmatic study’<sup>14</sup>, where subjects are managed according to their investigator’s usual care following randomization, and in conjunction with the protocol directed schedule of activities.

Data from 15 completed or on-going Phase 2/3 studies in over 29,000 subjects provide exposure information of apixaban doses ranging from 2.5 mg twice a day (BID) to 20 mg once daily (QD) and treatment durations up to approximately 33 months.

The posology of apixaban has been determined from its pharmacokinetic characteristics and per the approved local label for the prevention of stroke and systemic embolism in subjects with non-valvular AF. In this protocol, investigators have an option to use a single loading dose of 10 mg (or 5 mg, if the subject meets the criteria for dose reduction as per the local label) followed by the approved regimen of 5 mg BID (or 2.5 mg BID) starting 12 hours later, to rapidly achieve steady-state exposure (see [Section 5.2.3.2](#) for further details) (Japan only: the loading dose is not an available option for those subjects participating in Japan). Based on simulations of the apixaban concentration versus time profile in AF patients, this regimen will result in Day 1 peak plasma concentration ( $C_{max}$ ) and area under the curve (AUC) values that are approximately 104% and 93% of steady-state values, respectively.

Further information for apixaban may be found in the approved local label (eg, United States Package Insert (USPI), Summary of Product Characteristics (SmPC)).

## **2. STUDY OBJECTIVES AND ENDPOINTS**

The study objective is to assess the occurrence of clinical endpoints in non-valvular AF subjects (ie, without rheumatic mitral valve disease, a prosthetic heart valve, or valve repair) indicated for cardioversion and treated with apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)).

### Clinical Endpoints

- Stroke.
- Systemic embolism.
- Major Bleeding.
- Clinically Relevant Non-Major Bleeding.
- All cause death.

Additional information will also be collected on:

- Cardioversion details: timing, type, attempts, and rhythm status.
- Length of in-hospital stay.
- Use of image guidance eg, TEE/TOE or CT.

This protocol will use an independent endpoint adjudication committee wherein, to maintain scientific integrity, adjudication of disease-related efficacy endpoints will be performed. For those serious adverse events (SAEs) that are handled as disease-related efficacy endpoints (which may include death), the endpoint adjudication committee, in coordination with the data monitoring committee (DMC), is responsible for ongoing analysis of these outcomes and for informing the sponsor of recommendations made (eg, to continue the study or to stop the study).

### **3. STUDY DESIGN**

This is a randomized, active controlled, parallel-group, open label study.

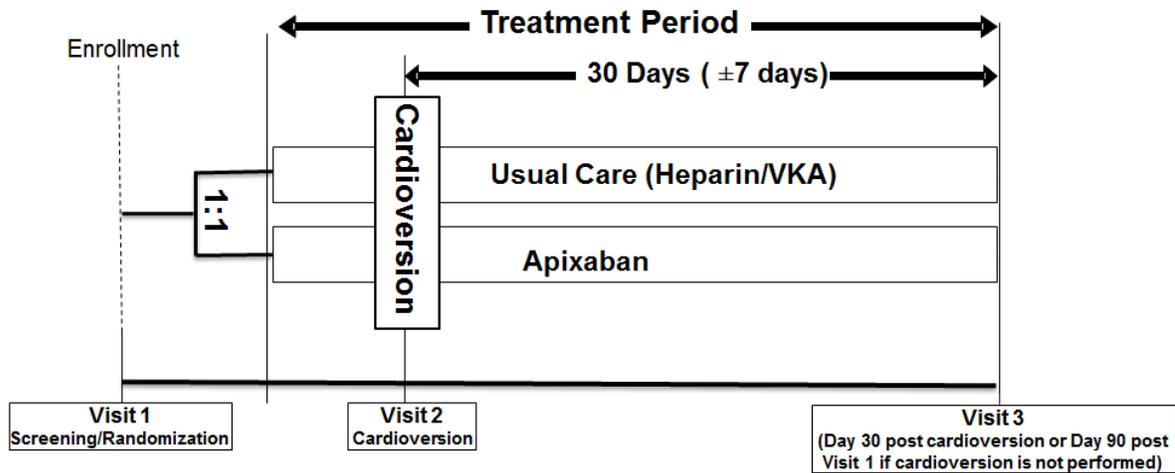
Approximately 1500 subjects will be randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)). Usual care will be administered as per local practice and/or approved label.

Apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other novel oral anticoagulants (NOACs))) will be administered from randomization up to 30 days following cardioversion or 90 days post randomization if cardioversion is not performed within that timeframe.

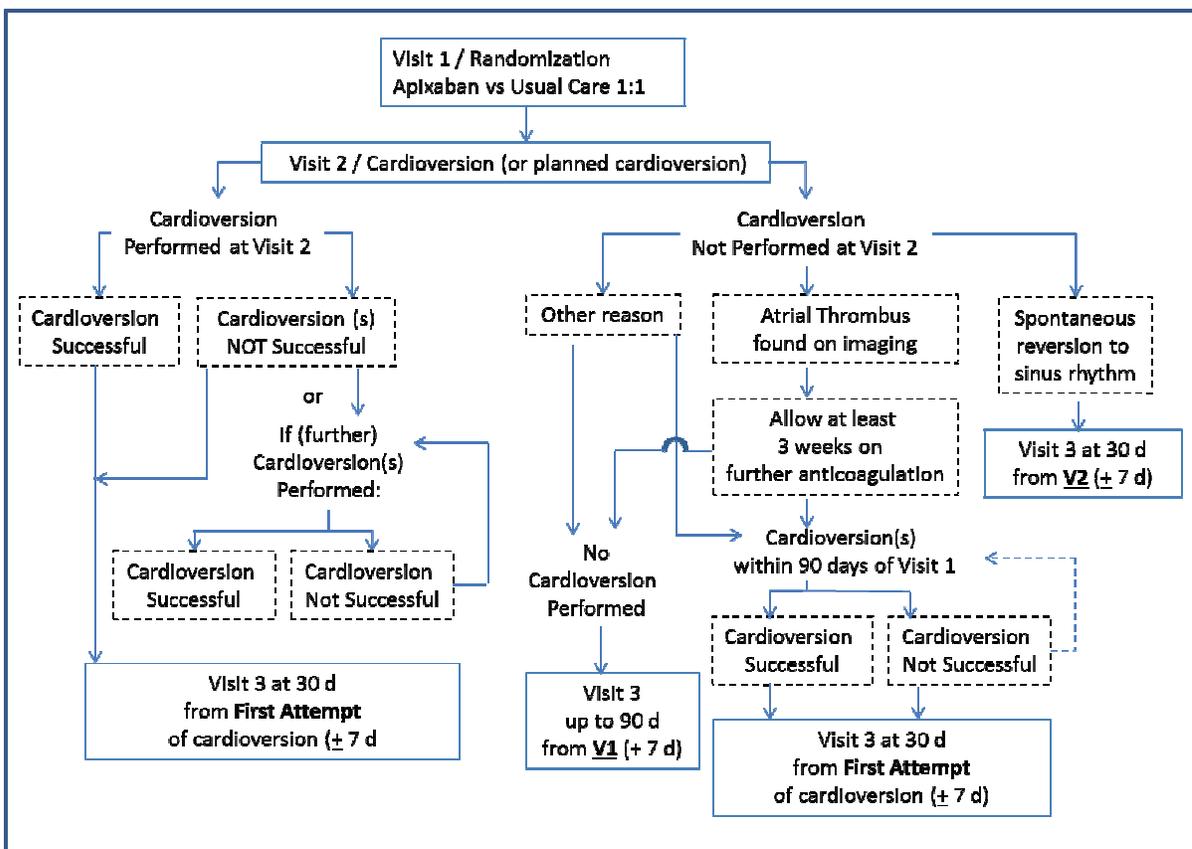
Following randomization, clinical endpoints, cardioversion details (timing, type, attempts, and rhythm status), length of in-patient hospital stay and use of image guidance will be collected during the 30 days following the cardioversion or during the 90 days post randomization if cardioversion is not performed.

A schematic diagram below (Figure 1) shows the design of the study:

**Figure 1 Study Design Schematic**



**Figure 2 Examples of Timing of Visit 3**



### **3.1. Executive Committee**

The Executive Committee will be composed of a group of clinical experts and sponsor representatives, responsible for ensuring that study design, execution and management are of the highest quality. The Executive Committee will provide suggestions for potential investigators and National Coordinators, will monitor progress of study enrollment, make recommendations in collaboration with the sponsor based on the DMC recommendations, and oversee the presentation and publication of the trial results. The membership, roles and responsibilities of the committee are further described in the Executive Committee Charter. The committee will convene regularly by teleconference and/or face-to-face meetings to discuss and report on the ongoing conduct of the study in collaboration with the sponsor.

## **4. SUBJECT SELECTION**

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

### **4.1. Inclusion Criteria**

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subjects with non-valvular atrial fibrillation (as documented by electrocardiogram (ECG) at Visit 1) indicated for cardioversion and initiation of anticoagulation in accordance with the approved local label. Subjects presenting with atrial flutter with no evidence of atrial fibrillation are not eligible for enrolment.
2. Age  $\geq 18$  years (Age  $\geq 19$  years for Korea only and Age  $\geq 20$  years for Japan only).
3. Evidence of a personally signed and dated informed consent document indicating that the subject (or their legally-recognized representative) has been informed of all pertinent aspects of the study.
4. The subject is willing to provide contact details for at least one alternate person for study staff to contact regarding their whereabouts, should the subject be lost-to-follow-up over the course of the study. (Subject to IRB/IEC approval)
5. Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active.
6. Subjects who are willing and able to comply with scheduled visits, treatment plan, and other study procedures.

## **4.2. Exclusion Criteria**

Subjects presenting with any of the following will not be included in the study:

1. Subjects having taken more than 48 hours of an anticoagulant (oral and/or parenteral) immediately prior to randomization.
2. Contraindications to apixaban or usual care (eg, VKA) in accordance with the approved local label.
3. Severe haemodynamically compromised subjects requiring emergent cardioversion.
4. Patients with hemodynamically significant mitral stenosis, mechanical or biological prosthetic valve or valve repair.
5. Conditions other than atrial fibrillation that require chronic anticoagulation (eg, a prosthetic heart valve).
6. Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine, prasugrel) or simultaneous treatment with both aspirin and ticagrelor.
7. Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.
8. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days before the current study begins and/or during study participation. Note: Subjects cannot be randomized into this study more than once.
9. Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
10. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are BMS/Pfizer employees directly involved in the conduct of the trial.

## **4.3. Life Style Guidelines**

Female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator will confirm that the subject enters the study already using a contraceptive method from the permitted list of highly effective contraceptive methods and has been instructed in its consistent and correct

use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

#### **4.4. Sponsor Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the trial will be documented in the study contact list located in the Investigator Site File. To facilitate access to appropriately-qualified medical personnel on study related medical questions or problems, subjects will be provided with a contact card. The contact card will contain, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

## **5. STUDY TREATMENTS**

### **5.1. Allocation to Treatment**

At Visit 1 subjects will be randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)). Treatment

group assignment will be managed using a centralized Internet-based or Interactive Voice Response System (IVRS).

## 5.2. Drug Supplies

### 5.2.1. Formulation and Packaging

Apixaban formulation and packaging details are as follows;

Product	Potency	Primary Packaging	Appearance	Storage
BMS-562247-01 Film Coated Tablet	5 mg	200 tablets per bottle  Open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2- 30°C
BMS-562247-01 Film Coated Tablet	2.5 mg	200 tablets per bottle  Open label	Reddish brown, plain, oval shaped, shallow bi-convex film coated tablet	Store at 2- 30°C

Usual care will be locally sourced, commercial drug supply provided via the investigator site; no packaging or labeling will be performed unless required by local country regulation.

Generally, the sponsor does not intend to cover the cost of usual care in this study. However, the decision to cover the cost of usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)) in each country will be made by the sponsor based on local requirements and guidelines.

### 5.2.2. Preparation and Dispensing

Sites should refer to the local package inserts for usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)) treatment for preparation and dispensing information.

Apixaban supplied to the Investigator must be stored in accordance with the clinical label and Investigators Brochure. Apixaban supplies must be stored separately from normal hospital/practice stocks. Until dispensed to the subjects, apixaban will be stored in a securely locked area, only accessible to authorized study personnel.

Usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)) treatment should be stored in accordance with the local label.

For subjects randomized to apixaban (or to the usual care arm, where usual care medication is stored at study site), the Investigator or delegate should dispense study drug treatment as per label and routine clinical practice, **and visually confirm the subject has received their medicine supply at randomization.**

For subjects randomized to the usual care arm, it is acceptable for the site to provide the subject with a prescription if this medication is not routinely stocked at the site and if this is consistent with routine clinical practice. In these events, visual inspection is ensured by review of the provided prescription.

A treatment log must be completed for either apixaban or usual care as appropriate.

### **5.2.3. Administration**

Apixaban or usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)) will be administered from randomization up to 30 days following first cardioversion attempt (or 30 days following Visit 2 in the event a subject has spontaneously reverted to normal sinus rhythm before cardioversion) or 90 days post randomization if cardioversion is not performed.

Administration details will be recorded in the case report form (CRF).

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

#### **5.2.3.1. Usual Care**

Usual care (parenteral heparin and/or oral anticoagulation with Vitamin K antagonist (excluding other NOACs)) will be administered as per local label/practice/guidelines.<sup>8,9</sup>

The dosing of the Vitamin K antagonist must be individualized according to the subject's sensitivity to the drug as indicated by their INR. INR monitoring should follow the investigators usual practice. All INR values during the study will be recorded in the CRF.

### 5.2.3.2. Apixaban

Apixaban will be administered and dose adjusted as per local label for the prevention of stroke and systemic embolism in subjects with non-valvular AF with provision of additional dosing guidance as detailed below:

If a subject randomized to apixaban is scheduled for an image guided cardioversion strategy, then at least 5 doses of apixaban 5 mg BID should be administered before the procedure is conducted to ensure steady-state exposure.

If the cardioversion must be conducted earlier than 5 doses of apixaban, a single 10 mg loading dose (administered as two 5 mg tablets) followed by 5 mg BID should be administered to achieve immediate steady-state exposure (Japan only: the loading dose is not an available option for those subjects participating in Japan and therefore at least 5 doses of apixaban should be administered before the image guided cardioversion is conducted). The cardioversion should not be performed until at least 2 hours following the loading dose administration.

If a subject meets the criteria for dose reduction, which are at least two of the following characteristics: age  $\geq 80$  years, body weight  $\leq 60$  kg, or serum creatinine  $\geq 1.5$  mg/dl (133 micromole/l) then 2.5 mg BID should be administered for at least 5 doses before cardioversion is conducted or a 5 mg loading dose followed by 2.5 mg BID (Japan only: the loading dose is not an available option for those subjects participating in Japan). Investigators should refer to their local label for dose adjustment guidance for subjects with severe renal impairment. For example the SmPC states "*Patients with exclusive criteria of severe renal impairment (creatinine clearance 15-29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily*".

A subject receiving an anticoagulant (oral and/or parenteral)  $\leq 48$  hours prior to screening may be randomized into the study. For subjects randomized to apixaban the transition from an anticoagulant (oral and/or parenteral) is as follows;

- Low molecular weight heparin (LMWH) - apixaban should be started at the time of next scheduled dose and no earlier than 12 hours after the previous parenteral anticoagulation administration. If an image guided cardioversion must be conducted earlier than 5 doses of apixaban, then, as directed above, the loading dose can be utilized.
- Unfractionated Heparin (UFH) - apixaban can be started between 0 to 2 hours after stopping intravenous unfractionated heparin. If an image guided cardioversion must be conducted earlier than 5 doses of apixaban, then, as directed above, the loading dose can be utilized.
- VKA - the VKA should be discontinued and apixaban started when the INR is below 2.0. If image guided cardioversion must be conducted earlier than 5 doses of apixaban, then, as directed above, the loading dose can be utilized. Details of INR will be recorded in the CRF.

- Oral anticoagulant other than a VKA - discontinue the oral anticoagulant being taken and begin apixaban at the next scheduled dose and no earlier than 12 hours after the previous oral anticoagulant administration. If an image guided cardioversion must be conducted earlier than 5 doses of apixaban, then, as directed above, the loading dose can be utilized.

#### **5.2.4. Compliance**

For subjects randomized to apixaban, compliance based on study drug tablet count will be recorded both at the time of cardioversion (Visit 2) and at Visit 3 for all subjects.

For subjects randomized to usual care, compliance is confirmed by ongoing INR monitoring. In addition, tablet count should be recorded both at the time of cardioversion (Visit 2) and at Visit 3 for all subjects where usual care has been dispensed directly by the site.

#### **5.3. Drug Storage and Drug Accountability**

Study drug should be stored in accordance with the label.

Investigators and site staff are reminded to check temperatures as per local practice (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of apixaban. Any temperature excursions should be reported to the sponsor.

Apixaban must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, apixaban must be quarantined and not used until the sponsor provides documentation of permission to use the product.

#### **5.4. Concomitant Medications**

Physicians should refer to the local package inserts for apixaban and usual care to guide prescribing of concomitant medications. The co-administration of parenteral heparin and apixaban is prohibited.

### **6. STUDY PROCEDURES**

#### **6.1. Visit 1 Enrollment, Screening/Randomization (can occur on the same day)**

##### **6.1.1. Screening Assessments**

The Investigator or designee will:

- Obtain written informed consent.
- Obtain alternate contact.
- Obtain subject demography.
- Obtain relevant medical history.

- Obtain Congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex category stroke risk score (CHA<sub>2</sub>DS<sub>2</sub>-VASc score).
- Assess and record local clinical laboratory parameters.
- Determine if subject meets inclusion/exclusion criteria, including confirmation of heart rhythm status from electrocardiogram (ECG). (ECG taken on the day prior to Visit 1 may be used for this assessment).

### 6.1.2. Randomization Assessments

The Investigator or designee will:

- Randomize subject using a centralized IVRS.
- Dispense study drug treatment as per label and routine clinical practice, and visually confirm the subject has received their medicine supply, see [Section 5.2.2](#).

### 6.2. Visit 2 Cardioversion

The Investigator or designee will:

- Assess and record clinical endpoints (stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding, and all cause death) and whether they meet the serious adverse event reporting criteria.
- Perform study drug treatment compliance check, see [Section 5.2.4](#).
- Assess and record local clinical laboratory parameters, including INR for VKA-treated subjects.
- Assess and record cardioversion details (timing, type, attempts, and rhythm status), and use of image guidance (eg, TEE/TOE or CT).
- Assess and record adverse events.
- Collect and dispense study drug treatment, if required, as per label and routine clinical practice, and visually confirm the subject has received their medicine supply, see [Section 5.2.2](#).

### 6.3. Visit 3 (30 days (±7) Post Cardioversion or 90 days (±7) Following Enrollment Visit 1 if Cardioversion is not Performed). See [Figure 2](#) for Further Examples of Timing of Visit 3.

The Investigator or designee will:

- Assess and record local clinical laboratory parameters, including INR for VKA-treated subjects.

- Assess and record ECG details
- Assess and record clinical endpoints (stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding and all cause death) and whether they meet the serious adverse event reporting criteria.
- Record length of in-hospital stay.
- Assess and record adverse events.
- Collect study drug treatment.
- Perform study drug treatment compliance check, see [Section 5.2.4](#).

#### **6.4. Subject Withdrawal**

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. If a subject is lost to follow-up, the enrolling physician (or designee) will attempt to contact the alternate contact.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

A subject who is withdrawn from the study is expected to be subsequently managed by their physician according to their usual practice. See also [Section 6.7](#).

#### **6.5. Guidelines for Image Guidance (eg, TEE/TOE or CT) Suggesting Atrial Thrombus**

The investigator should follow their usual practice, and in accordance with local and national guidelines. Positive TEE/TOE or CT will be submitted for adjudication.

It is expected that in the event of imaging suggesting atrial thrombus, that any cardioversion attempt would be deferred for a minimum period of at least 3 weeks of further anticoagulation, consistent with local/national guidelines. It would also be expected that repeat imaging would take place prior to consideration of further cardioversion attempts.

## 6.6. Guidelines for Bleeding/Suspected Bleeding

For subjects with clinically significant bleeding, the anticoagulant should be discontinued. Bleeding should be managed according to local standard of care and may include measures such as surgical haemostasis, volume resuscitation, and transfusion of blood products as deemed appropriate and in keeping with the treating physician's clinical judgment.

There is no specific antidote to reduce apixaban activity. Investigators should refer to the local prescribing information for further advice on significant bleeding that may occur on apixaban.

## 6.7. Treatment Transition Guidelines

At the end of the study or upon subject withdrawal it is expected that subsequent management and treatment for the subject will be conducted by their physician according to their usual practice and preferred treatment.

If switching anticoagulation treatment is required, then this will be managed in accordance with the local label.

For example, the USPI states *“Switching from warfarin to ELIQUIS: Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0”, “Switching from ELIQUIS to warfarin: ELIQUIS affects INR, so that INR measurements during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue ELIQUIS and begin both a parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range” and “Switching between ELIQUIS and anticoagulants other than warfarin: Discontinue one being taken and begin the other at the next scheduled dose”.*

The SmPC states *“Switching from Vitamin K antagonist (VKA) therapy to Elixquis: When converting patients from Vitamin K antagonist (VKA) therapy to Elixquis, discontinue warfarin or other VKA therapy and start Elixquis when the international normalized ratio (INR) is < 2.0” and “Switching from Elixquis to VKA therapy: When converting patients from Elixquis to VKA therapy, continue administration of Elixquis for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Elixquis with VKA therapy, obtain an INR prior to the next scheduled dose of Elixquis. Continue coadministration of Elixquis and VKA therapy until the INR is ≥ 2.0”*

For other countries, the local approved label should be referred to for advice.

## 7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document as soon as possible the reason for this and any corrective and

preventive actions which he/she has taken to ensure that normal processes are adhered to. The study team will be informed of these incidents in a timely fashion.

### **7.1. Demography**

Age, gender and race will be captured within the CRF at Visit 1.

### **7.2. Medical History**

Pertinent AF and other relevant medical history will be captured within the CRF at Visit 1. It is expected that subjects will have routine work-up at presentation according to the investigator's usual practice, with a minimum expectation of ECG confirmation of AF diagnosis. At Visit 1, an ECG to confirm AF does not need to be repeated for the protocol, if it was taken on the day prior to, or the same day as Visit 1.

### **7.3. CHA<sub>2</sub>DS<sub>2</sub>-VASc Score**

The CHA<sub>2</sub>DS<sub>2</sub>-VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex category) stroke risk score assigns 2 points age over 75 years and for a history of stroke or transient ischemic attack (TIA), and 1 point each for recent congestive heart failure, a history of hypertension, diabetes, vascular disease, age 65-74 years or sex category (ie, female gender). The summed score quantifies the risk of stroke in subjects with AF.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score will be assessed and the category scores will be captured within the CRF at Visit 1.

### **7.4. Clinical Endpoints**

Clinical endpoints will be assessed by the Investigator to determine whether they meet the protocol criteria as described below. Clinical events meeting the criteria will be recorded on the CRF and independently adjudicated.

#### **7.4.1. Acute Stroke**

An acute stroke is defined as a new, focal neurological deficit of sudden onset, lasting at least 24 hours, that is not due to a readily identifiable non-vascular cause (ie, brain tumor, trauma). All strokes during the study will be assessed and classified as primary hemorrhagic, non-hemorrhagic, infarction with hemorrhagic conversion, or unknown, as defined by the American College of Cardiology (ACC):

- **Primary hemorrhagic:** a stroke with documentation on imaging [eg, computed tomographic (CT) scan or magnetic resonance imaging (MRI)] of hemorrhage in the cerebral parenchyma, or a subdural or subarachnoid hemorrhage. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis.
- **Non-hemorrhagic:** a focal neurological deficit that results from a thrombus or embolus (and not due to hemorrhage) that appears and is still partially evident at 24 hours.

- Infarction with hemorrhagic conversion: no evidence of hemorrhage on an initial scan but appeared on a subsequent scan.
- Unknown type/no imaging performed: the type of stroke could not be determined by imaging or other means (lumbar puncture, neurosurgery).

#### **7.4.2. 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.

#### **7.4.3. Major Bleeding**

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 (eg, ultrasound (US), CT, MRI).

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

Major bleeding is defined as clinically overt bleeding that is accompanied by one or more of the following:

- A decrease in hemoglobin (Hgb) of 2 g/dL or more
- 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.

#### **7.4.4. Clinically Relevant Non-Major Bleeding**

The definition of clinically relevant non-major bleeding will be clinically overt bleeding that consists of:

- Any bleeding compromising hemodynamics.
- Any bleeding leading to hospitalization.
- Subcutaneous hematoma larger than 25 cm<sup>2</sup>, or 100 cm<sup>2</sup> if there was a traumatic cause.
- Intramuscular hematoma documented by ultrasonography.
- Epistaxis that lasted for more than 5 minutes, was repetitive (ie, two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (eg, packing or electrocoagulation).
- Gingival bleeding occurring spontaneously (ie, unrelated to eating or tooth brushing) or lasting for more than 5 minutes.
- Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (eg, catheter placement or surgery) of the urogenital tract.
- Macroscopic gastrointestinal hemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult-blood test.
- Rectal blood loss, if more than a few spots on toilet paper.
- Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism or:
  - Any other bleeding type considered to have clinical consequences for a subject, such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug; or
  - Associated with pain or impairment of activities of daily life.

#### **7.5. Details of Cardioversion**

The date and time of all attempted cardioversion procedures and rhythm status according to ECG analysis will be captured within the CRF at Visit 2 and Visit 3. The performance of ECG monitoring is in accordance with the investigator's usual practice, and it is expected this would be performed pre and post cardioversion procedures at appropriate times.

Attempts are defined as the number of times the subject is admitted for the cardioversion procedure and not the number of attempts during a single admission.

## **7.6. Length of In-Hospital Stay**

Length of in-hospital stay is defined as the number of hours from hospital admission to hospital discharge following early cardioversion.

The date and time of all hospital admissions and discharges following cardioversion will be captured within the CRF at Visit 2 and 3.

## **7.7. Collection of Local Clinical Laboratory Parameters**

Local clinical laboratory assessments should be performed as part of the routine care for subjects undergoing cardioversion at the clinical practice.

From these routine assessments hemoglobin and serum creatinine will be recorded within the CRF from Visit 1 to Visit 3.

## **8. ADVERSE EVENTS**

In this clinical protocol adverse and serious adverse event reporting will be managed according to the following BMS standard operating definitions and procedures.

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

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). 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 AEs).

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and Food and Drug Administration (FDA) Code of Federal Regulations 21 CFR Parts 312 and 320.

### 8.1. Serious Adverse Events

A *Serious Adverse Event (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**);
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- 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 [eg, 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). Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 8.6](#) for the definition of potential DILI).

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

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See [Section 8.1.1](#) for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE (see [Section 8.1.1](#) for reporting details).

#### **NOTE:**

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

- a visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered an important medical or life-threatening event);
- elective surgery, planned prior to 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 to remedy ill health and 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

### **8.1.1. Serious Adverse Event Collection and Reporting**

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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 discontinuation of dosing.

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

An SAE report must be completed for any event where doubt exists regarding its 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 must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic case report form (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** Refer to [Contact Information list](#).

**SAE Facsimile Number:** Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted 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.

## **8.2. Nonserious Adverse Events**

A *nonserious adverse event* is an AE not classified as serious.

### **8.2.1. Nonserious Adverse Event Collection and Reporting**

The collection of nonserious AE information should begin at initiation of study drug. 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.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see [Section 8.1.1](#)). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

## **8.3. Laboratory Test Result Abnormalities**

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- 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 laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

#### **8.4. 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 study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 8.1.1](#).

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor/designee within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 8.1.1](#).

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS (or designee). Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

#### **8.5. Overdose**

All occurrences of overdose must be reported as SAEs (see [Section 8.1.1](#) for reporting details).

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 an SAE (see [Section 8.1.1](#) for reporting details).

#### **8.6. Potential Drug Induced Liver Injury (DILI)**

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs must be reported as SAEs (see [Section 8.1.1](#) for reporting details).

## **8.7. Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be developed in collaboration between the Executive Committee and the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### **9.1. Sample Size Determination**

The study is intended to be descriptive only. The study will enroll approximately 1500 subjects. No power calculation was performed but with a sample size of 1500 subjects, and based upon an ARISTOTLE warfarin naive cohort of subjects (the closest analogous data-set to this study design), the predicted incidence of stroke and systemic embolism within 30 days post cardioversion is approximately 0.3% (1 event on apixaban and 3 events on usual care). Similarly, the predicted event rate for major bleeding is approximately 0.45% (2 events on apixaban and 5 events on usual care).

For a study of this type, in order to adequately power for statistically significant claims, about 480 endpoints would be needed (similar to the ARISTOTLE trial).<sup>10</sup> However, due to the limited relevant follow-up (30 days following cardioversion or 90 days post randomization), and a clinical estimate for event rate of approximately 1% this would require approximately 48000 subjects, which would not be a feasible study.

### **9.2. Endpoint Analysis**

This is a descriptive study, and there is no formal pre-defined hypothesis testing.

Baseline demographics, endpoints, AEs and SAEs will be reported by randomized treatment arm as per Pfizer/BMS reporting standards and consistent with the therapeutic area standards. Number of observations and proportions will be given for categorical or binary variables, number of observations, mean, standard deviation, median minimum and maximum will be given for continuous variables; time-to-event data will be displayed using Kaplan-Meier techniques; hazard ratio will be calculated.

### **9.3. Data Monitoring Committee**

This study will use a Data Monitoring Committee (DMC) independent of the sponsor study team. The sponsor study team will monitor blinded data trends in accordance with the Safety Review Plan.

The DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of

the study will be forwarded to Executive Committee and the sponsor (Pfizer/BMS) for final decision. The sponsor will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

#### **9.4. Independent Adjudication**

Independent Adjudicator(s) will review and adjudicate all clinical endpoints and positive TEE/TOE or CT without awareness of treatment allocation, ie, in a blinded manner. The responsibilities and procedures followed are described in the Adjudication Charter.

### **10. QUALITY CONTROL AND QUALITY ASSURANCE**

During study conduct, Pfizer/BMS or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer/BMS monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer/BMS, or companies working with or on behalf of Pfizer/BMS, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

### **11. DATA HANDLING AND RECORD KEEPING**

#### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer/BMS and should not be made available in any form to third parties, except for authorized representatives of Pfizer/BMS or appropriate regulatory authorities, without written permission from Pfizer/BMS.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer/BMS and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer or BMS, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer and BMS should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer/BMS, such as another investigator, another institution, or to an independent third party arranged by Pfizer/BMS. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer/BMS's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer/BMS.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer/BMS in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the [International Ethical Guidelines for Biomedical](#)

[Research Involving Human Subjects](#) (Council for International Organizations of Medical Sciences 2002), [Guidelines for GCP](#) (ICH 1996), and the [Declaration of Helsinki](#) (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer/BMS in order to de-identify the trial subject. In case of data transfer, Pfizer/BMS will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

### **12.4. Subject Recruitment**

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer and/or BMS should be informed immediately.

In addition, the investigator will inform Pfizer and/or BMS immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in a Member State**

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

#### **13.2. End of Trial in all other Participating Countries**

End of Trial in all other participating countries is defined as Visit 3.

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer/BMS. In addition, Pfizer/BMS retains the right to discontinue development of apixaban at any time.

If a study is prematurely terminated or discontinued, Pfizer/BMS will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 48 hours. As directed by Pfizer/BMS, all study materials must be collected and all CRFs completed to the greatest extent possible.

### **15. PUBLICATION OF STUDY RESULTS**

#### **15.1. Communication of Results by Pfizer/BMS**

Pfizer/BMS fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer/BMS in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer/BMS posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer/BMS-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer/BMS product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

*Primary Completion Date* is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome,

whether the clinical trial concluded according to the pre-specified protocol or was terminated.

### EudraCT

Pfizer/BMS posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

[www.pfizer.com](http://www.pfizer.com)

Pfizer/BMS posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer/BMS-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **15.2. Publications by Investigators**

Pfizer/BMS has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected Inventions, Investigator will provide Pfizer/BMS an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer/BMS at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multi-centre study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

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Final Protocol Amendment, 22 February 2016

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Publication of study results is also provided for in the Clinical Study Agreement between Pfizer/BMS and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

## 16. REFERENCES

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