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The AEIOU Trial: **A**pixaban **E**valuation of **I**nterrupted **O**r **U**ninterrupted Anticoagulation for Ablation of Atrial Fibrillation

CV185-373

Protocol

Version 1.1

September 2, 2015

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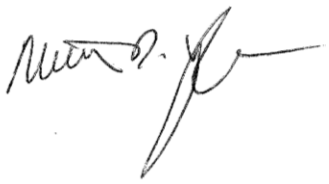
Document History

Revision	Author	Date reviewed/ revised	Changes	Reason for Changes
1.0	Joanna Suomi	April 2, 2015	New document	N/A
1.1	Priscilla Driscoll Shempp	September 2, 2015	Minor edits to language describing retrospective cohort, enrollment window for prospective cohort and addition of study schema	Clarification

STUDY PRINCIPAL INVESTIGATOR SIGNATURE PAGE

The undersigned have reviewed and approved the following protocol:



9/4/2015

Matthew Reynolds, MD, MSc
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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Clinical Investigation Protocol No. _____

I have reviewed this protocol for the study entitled:

The AEIOU Trial: Apixaban Evaluation of Interrupted Or Uninterrupted Anticoagulation for Ablation of Atrial Fibrillation

I agree to conduct this study according to the requirements described in the protocol.

Investigator Name (print or type): _____

Investigator's Signature: _____

Date: _____

Site Number: _____

Site Address: _____

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LIST OF APPENDICES

1 PROTOCOL SYNOPSIS

STUDY TITLE	Apixaban Evaluation of Interrupted Or Uninterrupted Anticoagulation in Ablation of Atrial Fibrillation.
PHASE	Phase IV
INTERVENTION	Apixaban uninterrupted therapy vs. interrupted therapy. Apixaban dose will be 5 mg b.i.d. (per product label, dose adjustment to 2.5 mg b.i.d. will be required for subjects with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL).
PROTOCOL NUMBER	CV185-373
STUDY DESIGN	Prospective, multicenter, randomized, open-label clinical trial. The study will compare 2 arms: uninterrupted vs. interrupted therapy with apixaban in subjects with planned catheter ablation for the treatment of nonvalvular atrial fibrillation (NVAF). Simultaneously, a retrospective cohort of 300 warfarin-treated individuals, identified by chart review, who are matched to the prospective randomized subjects, will be identified. Key demographic and outcome variables from each patient record will be documented. The outcomes in this group will be compared to the outcomes in the randomized, prospective cohort.
OBJECTIVES	For the prospective, randomized cohort: to evaluate the efficacy and safety of apixaban uninterrupted therapy vs. interrupted therapy during the peri- and post-procedural period of catheter ablation. For the retrospective, warfarin cohort: to assess the efficacy and safety of apixaban compared to the current clinical setting (use of warfarin). Outcomes derived from the retrospective warfarin cohort will be compared to that observed in the combined (both randomized arms) prospective cohort, and to that observed in each randomized arm of the prospective cohort (warfarin vs. uninterrupted apixaban; warfarin vs. interrupted apixaban).
HYPOTHESES	A strategy of uninterrupted apixaban will have similar rates of bleeding and thrombotic events as an interrupted strategy. Peri- and post-procedural treatment with apixaban may have a similar risk

	of thrombotic events but with a decreased risk of bleeding compared with current peri- and post-procedure anticoagulation management strategies with warfarin.
SUBJECT POPULATIONS	For the prospective, randomized cohort: Subjects undergoing catheter ablation for NVAF. For the retrospective, warfarin cohort: Patient records identified through chart review of individuals who underwent catheter ablation for NVAF on or after September 1, 2013 in the enrolling centers, who were treated with warfarin, who have documented follow-up in the medical record for ≥ 30 days post-ablation procedure, and who are matched (prospectively, with site personnel blinded to the clinical outcome) to the prospective, randomized cohort for age (+/- 5 years), gender, and AF type (paroxysmal vs. persistent).
STUDY PROTOCOL	For the prospective, randomized cohort: Subjects undergoing catheter ablation for NVAF will be enrolled prospectively. Subjects will be treated with apixaban for ≥21 days prior to ablation. Apixaban dose will be 5 mg b.i.d.; per product label, dose will be 2.5 mg b.i.d. in subjects with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Subjects will be randomized 1:1 to 2 peri-procedural treatment strategies: 1. Uninterrupted treatment: administer the evening apixaban dose on the day prior to the procedure; administer the morning apixaban dose on the day of the procedure; administer heparin bolus before transseptal puncture to maintain a target activated clotting time (ACT) > 300 seconds; administer the evening apixaban dose after the procedure if there were no peri-procedural complications that necessitate withholding anticoagulation for longer duration. 2. Interrupted treatment: administer the evening apixaban dose on the day prior to the procedure; ***do not*** administer the morning apixaban dose on the day of the procedure; administer heparin bolus before transseptal puncture to maintain a target ACT > 300 seconds; administer the evening apixaban dose after the procedure if there were no peri-procedural complications that necessitate withholding anticoagulation for longer duration. Subjects will be consented and enrolled at Visit 1 and treated with apixaban; for subjects already being treated with apixaban for ≥21 days, it is not necessary to wait 21 days between Visit 1 and Visit 2. Eligible subjects will be randomized prior to the procedure (Visit 2); randomization may take place on the day of the procedure or up to 3 days

	prior. Subjects not randomized will be considered screen failures. Routine monitoring, including pre-procedural transesophageal echocardiography, will be performed at the discretion of the investigator. Randomization of subjects will be stratified only by site. Apixaban treatment will be continued for 1 month post-catheter ablation. Visits will be at screening/enrollment, pre-procedure, discharge, and at 1 month for follow-up. For the retrospective, warfarin cohort: A chart review will be conducted to identify patient records for 300 warfarin-treated individuals who underwent ablation for NVAF on or after September 1, 2013 in the enrolling centers, who have documented follow-up in the medical record for ≥ 30 days post-ablation procedure, and who are matched to the subjects from the prospective randomized cohort. Site personnel will prospectively review (blinded to the subject's clinical outcome) matched records of patients who meet the applicable inclusion/exclusion criteria (see Inclusion/Exclusion Criteria for details) to document key demographic and outcome variables. This review will assess the incidence of the adjudicated primary endpoint in the current setting. Only pre-existing data will be collected for the analysis of this cohort.
NUMBER OF SUBJECTS AND SITES	Up to 20 sites in the United States (US) will participate. For the prospective, randomized cohort: In order to obtain 300 randomized subjects, it is anticipated that up to 360 subjects will be enrolled. For the retrospective, warfarin cohort: 300 matched patient records will be identified via retrospective chart review, with site personnel blinded to the subject outcome.
PRIMARY ENDPOINTS	Primary safety endpoint: The primary safety endpoint is the incidence of clinically significant bleeding assessed from the time of randomization through 1 month post–catheter ablation. *Clinically significant bleeding* is defined as bleeding meeting Bleeding Academic Research Consortium (BARC) criteria type 2 or higher. See Appendix 2 for BARC definitions. Primary efficacy endpoint: The primary efficacy endpoint is the incidence of thrombotic events assessed from the time of randomization through 1 month post-catheter ablation. *Thrombotic events* are defined as

	a composite of non-hemorrhagic stroke and systemic thromboembolic events.
SECONDARY ENDPOINTS	*Major Secondary Endpoints* Incidence of a composite of major bleeding (defined as BARC criteria type 3 or higher) and thrombotic events assessed from the time of randomization and from the time of enrollment through 1 month post–catheter ablation. Incidence of a composite of clinically significant bleeding (BARC criteria type 2 or higher) and thrombotic events assessed from the time of randomization and from the time of enrollment through 1 month post–catheter ablation. See protocol for *Additional Secondary Endpoint* information.
SUBGROUP ANALYSES	The primary and major secondary endpoints will be assessed for the following major subgroups: a. Age (<80 and ≥80 years). b. CHA_2DS_2-VASc (Congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category) score (< median, ≥ median). c. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) and $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke) bleeding risk scores (< median, ≥ median). d. Baseline antiplatelet therapy vs. no antiplatelet therapy. e. Baseline anticoagulation therapy (subjects who are anticoagulation-naïve versus subjects on vitamin K antagonists versus subjects on novel oral anticoagulants). f. Subjects with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. g. Apixaban dose.

SAMPLE SIZE CONSIDERATIONS AND STATISTICAL ANALYSES

Given the nature of the pilot study, it is not powered for the primary analyses of comparing randomized treatments on the primary endpoints. The sample size however is based on an evaluation of anticipated event rates as compared with current literature, as described further below. While not definitively powered to detect differences in the randomized groups, this study should provide useful information on this patient population.

For the primary analysis of the comparison of the interrupted versus uninterrupted apixaban treatment strategies, the primary efficacy and safety endpoint rates and the exact 2-sided 95% confidence intervals of the primary efficacy and safety endpoints for each apixaban group (and for both apixaban groups combined) and a 2-sided 95% confidence interval of the risk difference between the apixaban groups (calculated using the Wilson method) will be displayed for apixaban-treated subjects.

In addition, the secondary analysis of the primary efficacy and safety endpoints will compare the rates (from randomization to 1 month post-ablation) of clinically significant bleeding events and of thrombotic events observed in the apixaban prospective randomized cohort (both randomized arms combined and separately by randomized arm), compared to that observed in the matched, retrospective warfarin cohort.

Sample size justification:

A tertiary but important current aim of the study is to assess the combined thrombotic/bleeding rate for both apixaban groups combined via an approach using a comparison to a literature-derived boundary. The boundary is derived from the warfarin event rates reported in studies assessing novel oral anticoagulants versus warfarin in the setting of ablation, and in which 3-month rates were reported. This strategy ensures the literature-derived boundary is reflective of current standards of care.

We searched PUBMED for the following search criteria: *"(dabigatran AND ablation) OR (rivaroxaban AND ablation) OR (apixaban AND ablation) OR (novel oral anticoagulants AND ablation).*" The search yielded 78 titles, of which 12 full-text articles were retrieved for in-depth review. The following 5 studies were identified:

Study	Warfarin Group Size	Clinically Significant Bleeding and Thrombotic Events*
Kaseno *et al.*[1]	101	13 (12.9%)
Bassiouny *et al.*[2]	623	24 (3.9%)
Kaiser *et al.*[3]	135	12 (8.9%)
Kim *et al.*[4]	572	31 (5.4%)
Yamaji *et al.*[5]	203	7 (3.4%)

* Includes thromboembolic events, major clinically significant bleeding events, and minor bleeding events.

A meta-analytic rate of the composite of clinically significant bleeding and thrombotic events is calculated to be 5.5% (±1.1%) from a random effects meta-analysis (random effects meta-analysis was used due to significant heterogeneity among studies).

Because most events will occur early after the index event, and to compare rates at 1 month (rather than 3 months in the literature), we will use a composite event rate of 5.0% for the apixaban group. Other recent studies, having differing definitions of major bleeding, have event rates ranging from 3% to 12%.[6-8] As such, a conservative 5% rate for the composite seems reasonable.

An analysis of the two randomized groups of apixaban combined (300 patients) will be used to assess whether the 1-month rate of the composite of clinically significant bleeding and thrombotic events (and additionally of the composite of major bleeding and thrombotic events) falls below a boundary of 8.7%. Specifically, this study will assess the ability of apixaban (in both randomized groups combined) in the setting of ablation to meet a boundary of 8.7%, which is an absolute increase of 3.7% over the expected rate of 5.0%.

The following assumptions were used for the sample size calculations:

- Assessment is that the incidence of a composite of clinically significant bleeding and thrombotic events (and composite of major bleeding and thrombotic events) in the setting of apixaban treatment (interrupted and uninterrupted combined) peri- and post-ablation for NVAF meets the boundary using a 1-sided exact test based on the binomial distribution.
- The true apixaban event rate at 1 month is assumed to be 5.0%.
- Type I error (α) = 0.05 (1-sided).
- Power of 80%.

	A sample size of 300 apixaban subjects in the prospective, randomized cohort provides 80% power to meet this boundary, with the upper bound of the 1-sided 95% confidence interval of the event rate in the study cohort not exceeding 8.7%.
INCLUSION CRITERIA	For the prospective, randomized cohort: 1. Signed 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 or their legal representatives will indicate that consent by signing and dating the informed consent document in the presence of study personnel. 2. ≥18 years of age. 3. NVAF with planned catheter ablation treatment. 4. Planned anticoagulant treatment for a minimum of 1 month after catheter ablation. 5. Subject agrees to all required follow-up procedures and visits. 6. For women of childbearing potential (WOCBP): • Must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study drug. • Must not be breastfeeding • Must agree to follow instructions for method(s) of contraception for the duration of treatment with the study drug apixaban plus 5 half-lives of apixaban (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion. 7. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with the study drug, apixaban, plus 5 half-lives of apixaban (3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion. 8. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as described in this section.

INCLUSION CRITERIA (CONTINUED)	For the retrospective, warfarin cohort: 1. ≥18 years of age, at the time of the historical catheter ablation procedure. 2. NVAF with catheter ablation treatment on or after September 1, 2013in the enrolling center. 3. Treatment with a strategy of "uninterrupted warfarin" prior to and following catheter ablation (i.e. no peri-procedural bridging with low molecular weight heparin). 4. Medical record includes documentation of follow-up for ≥ 30 days post-ablation, i.e. follow-up visit or phone contact (at the facility or with other medical provider). 5. Baseline characteristics in patient record match 1:1 with a subject in the prospective, randomized cohort within the same study site, based on all of the following criteria: • Age (+/– 5 years) • Gender • AF type (paroxysmal vs. persistent).
EXCLUSION CRITERIA	For the prospective, randomized cohort: 1. History of significant bleeding diathesis or coagulopathy or inability to accept blood transfusions. 2. Known hypersensitivity or contraindication to heparin or apixaban. 3. Subjects with mechanical prosthetic heart valves. 4. History of cerebrovascular accident or transient ischemic attack within the last 6 months. 5. Prior intracranial hemorrhage. 6. End-stage renal failure (creatinine clearance rate <15 mL/minute or on dialysis treatment). 7. Hepatic disease associated with coagulopathy. 8. Current or expected systemic treatment with strong dual inducers of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's wort). 9. Current or expected systemic treatment with dual antiplatelet therapy, other anticoagulants, or fibrinolytics. 10. Planned or expected surgery, or other invasive procedure that would require interruption of anticoagulation within 1 month of

EXCLUSION CRITERIA (CONTINUED)	the catheter ablation procedure. 11. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints. 12. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or that could impact the scientific integrity of the trial. 13. Platelet count ≤100,000/mm^3. 14. Hemoglobin level <9 g/dL. 15. Any active bleeding. 16. Prisoners or subjects who are involuntarily incarcerated. 17. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness. <u>For the retrospective, warfarin cohort</u>: Exclusion criteria 1-15 apply to this study population, applicable at the time of the historical catheter ablation procedure.
ESTIMATED START DATE, ENROLLMENT, AND FOLLOW-UP	Estimated start date is in the third quarter of 2015. The enrollment phase is expected to last 10 months. Subjects will be followed from enrollment (approximately 0-42 days prior to ablation) to 1 month post-procedure.

2 INTRODUCTION

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is associated with substantial mortality and morbidity.[9] The estimated prevalence of AF is 0.4% to 1% in the general population, and increases with age.[9,10] AF is also associated with increased morbidity and increased risk of thrombotic embolism and death.[11-13] The rate of ischemic stroke among patients with nonvalvular atrial fibrillation (NVAF) is estimated at 5% per year,[14] with 1 of every 6 strokes occurring in a patient with AF.[15] The use of antithrombotic medications can mitigate some of the embolic risks associated with AF, and clinical guidelines recommend that anticoagulants be used in patients with more than 1 moderate risk factor.[14]

Catheter ablation of AF has become a well-established therapeutic approach in symptomatic patients.[14] However, AF catheter ablation is technically challenging and carries a risk of thromboembolic complications, likely associated with the catheters used in the left atrium, endothelial denudation, scar formation, and tissue inflammation.[16-18] The incidence of thromboembolic events associated with AF ablation can be as high as 7%,[19] and there are reports indicating clinically silent cerebral microembolism detected only by post-procedural imaging.[20,21] Peri-procedural anticoagulation management in patients undergoing AF ablation can mitigate some of these effects, but is associated with a higher bleeding rate.[22] Recent guidelines suggest that catheter ablation of AF can be executed without warfarin interruption, but the level of evidence supporting this recommendation is still low.[23]

The field of anticoagulation has changed considerably over the last few years. Considerable research has sought to overcome the limitations of available anticoagulant and antithrombotic agents, including efforts to develop agents that target specific factors of the coagulation process, which in turn may improve efficacy and increase the therapeutic index. Factor Xa (FXa) is a primary target, as this factor plays a pivotal role in the coagulation cascade at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is expected to exert anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.[24]

Novel oral anticoagulants (NOACs) have been studied for treatment of AF in the setting of catheter ablation. They have shown to carry a comparable risk-benefit profile to that of warfarin.[25,26] Apixaban, a novel, orally active, potent, direct selective inhibitor of coagulation FXa, reversibly binds to the active site of FXa, and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. It has been shown to reduce the risk of stroke, systemic embolism, and bleeding in patients with AF compared with

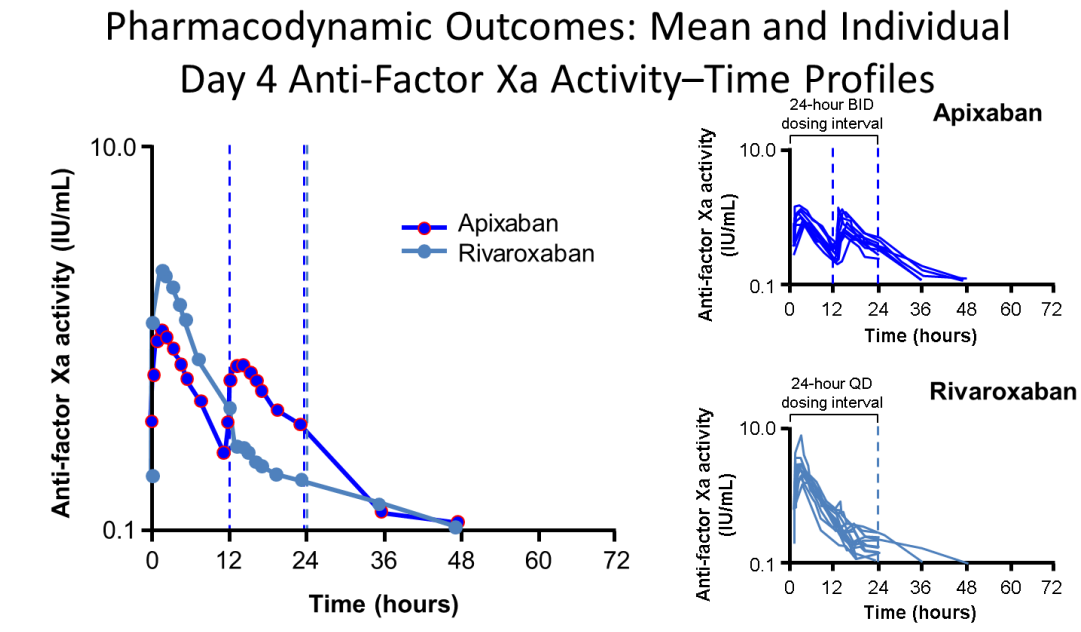
warfarin,[27] and reduce the risk of stroke and systemic embolism without increasing the risk of bleeding compared with aspirin in patients for whom vitamin K antagonists are not suitable.[24]

Considerable uncertainty exists about the optimal strategy for dosing NOAC agents around the time of an ablation procedure. "Uninterrupted" warfarin has become the standard approach based on case series and on randomized study (BRUISE CONTROL) of a related procedure[28-31]

A series of papers have been published using uninterrupted rivaroxaban, with similar rates of bleeding and thrombotic endpoints as warfarin control patients.[26] With dabigatran, two strategies of interrupted dosing have been evaluated in prior years, where holding one dose was associated with increased bleeding, but holding two doses was not. Randomized trials however, are testing an uninterrupted strategy.[32 33]

With apixaban, the graph below illustrates the level of anticoagulation over time with twice daily dosing, which would be that of an "uninterrupted" strategy. For an "interrupted" strategy, holding the dose in the morning of the ablation procedure, thus being between 12-18 hours following a dose (if last taken at 8pm the night before) – the level of anticoagulation approximates that of rivaroxaban. Which of these two approaches gives the best overall effectiveness for avoiding bleeding and thrombotic complications is unknown.[34]

Apixaban vs Rivaroxaban PK/PD



- A close temporal relationship between plasma concentration and anti-factor Xa activity was seen for both compounds across the dosing interval

Anti-factor Xa activity is given in low molecular weight heparin units per mL

BID, twice daily; QD, once daily

2.1 Overall Risk/Benefit Assessment

Similar to other NOACs, apixaban is expected to have a risk-benefit profile that is comparable to that of warfarin in subjects with NVAF undergoing radiofrequency ablation. In this study, peri- and post-procedural treatment with apixaban may reduce procedure-related risk of thromboembolic complications but with a decreased risk of bleeding compared with current peri- and post-procedure anticoagulation management strategies.

Between the two dosing strategies, it is not known whether the uninterrupted or interrupted strategy of apixaban will differ in their rates of clinically significant bleeding or thrombotic events. For possible benefits and risks – holding one dose of apixaban could potentially lower the risk of bleeding or might increase thrombotic events; conversely, continuing apixaban might lead to a higher risk of bleeding but lower rates of thrombotic events. On balance though, with the modest difference in the level of anticoagulation, it is hypothesized that the rates of these events will be similar between the two strategies.

2.2 Research Hypothesis

For the prospective, randomized cohort:
Among subjects planned to undergo catheter ablation for treatment of NVAF, it is hypothesized that the incidence of thrombotic events and bleeding events will be similar between the two arms of the study (apixaban uninterrupted therapy vs. apixaban interrupted therapy). To assess this hypothesis, the primary efficacy and safety endpoint rates and the exact 2-sided 95% confidence intervals of the primary efficacy and safety endpoints for each apixaban group (and for both apixaban groups combined) and a 2-sided 95% confidence interval of the risk difference between the groups (calculated using the Wilson method) will be presented for apixaban-treated subjects.

Retrospective warfarin cohort:
It is hypothesized that peri- and post-procedural treatment with apixaban may have similar risk of thrombotic events but with a decreased risk of bleeding compared with current peri- and post-procedure anticoagulation management strategies with warfarin.

A tertiary research hypothesis is:
The combined clinically significant bleeding and thrombotic event rate (and additionally the combined major bleeding/thrombotic event rates) with apixaban peri- and post-procedural

treatment (interrupted and uninterrupted combined) will be lower than the literature-based boundary of 8.7% at 1 month based on the medical literature. To assess this hypothesis, we will compare the 1-sided 95% upper bound of the confidence interval of the rate of clinically significant bleeding and thrombotic events to the literature-based boundary. (If interrupted and uninterrupted apixaban are considered to be statistically and clinically significantly different on the combined bleeding/thrombotic event rate, then this analysis may be carried out separately for interrupted and uninterrupted apixaban).

2.3 Study Rationale

This post-market, prospective, randomized trial is designed to assess the efficacy and safety of apixaban in subjects planned to undergo catheter ablation for treatment of NVAF. This will be the first study addressing the safety and efficacy of 2 apixaban treatment strategies (uninterrupted versus interrupted) in the setting of NVAF ablation. It will also assess the effectiveness of each strategy for apixaban (uninterrupted, interrupted) versus warfarin and both strategies for apixaban combined (uninterrupted plus interrupted) versus warfarin.

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2.4 Study Objectives

For the prospective, randomized cohort: to evaluate the efficacy and safety of apixaban uninterrupted therapy vs. interrupted therapy during the peri- and post-procedural period of catheter ablation.

For the retrospective, warfarin cohort: to assess the efficacy and safety of apixaban compared to the current clinical setting (use of warfarin). Outcomes derived from the retrospective, warfarin cohort will be compared to that observed in the combined (both randomized arms) prospective cohort, and to that observed in each randomized arm of the prospective cohort (warfarin vs. uninterrupted apixaban; warfarin vs. interrupted apixaban).

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 (CFR), 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 immediately to Harvard Clinical Research Institute (HCRI). 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 (e.g., 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 (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the product labeling information to be provided to subjects, and any updates. HCRI must receive a letter documenting the IRB/EC approval prior to initiation of the study.

The investigator should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures. The investigator is also responsible for informing the IRB/EC of the progress of the study and for obtaining annual IRB/EC renewal. The IRB/EC must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the site principal investigator (PI). The investigator must notify the IRB/EC in writing of any serious adverse event or any unexpected adverse event according to ICH guidelines.

3.3 Informed Consent

The following information in this section applies to the prospective, randomized cohort only:

The investigator must comply with informed consent regulations (U.S. 21CFR Part 50), ICH/GCP Guidelines, the Declaration of Helsinki, and relevant state regulations (i.e., California Bill of Rights for California patients). The ICF must be reviewed and approved by the site investigator's designated IRB/EC and by HCRI. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6). Each site must provide HCRI with a copy of the study site's IRB/EC approval letter and the approved ICF. Investigators must ensure that subjects or, in situations in which consent cannot be given by subjects, their legally acceptable representative, 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 the subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent that is signed and personally dated by the subject or the subject's legally acceptable representative 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 (ICF) 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. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6. 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 or the subject's legally acceptable representative or legal guardian, 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.

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

Any revisions to the approved ICF must be reviewed and approved by HCRI before submission to the IRB/EC.

3.4 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the written information provided to the subject. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the subject. The study data shall not be disclosed to a third party without the written consent of the sponsor.

Subject confidentiality will be maintained throughout the clinical study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated as confidential and that the subject's privacy is guaranteed.

"Protected Health Information" will be treated and maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) privacy rule and applicable local laws on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

The duration of storage time of personal data at the investigational sites will be in accordance with national regulations (see Section 12.2).

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

4.1.1 Prospective, Randomized Cohort

Subjects undergoing ablation for NVAF will be screened for eligibility and those meeting all eligibility requirements (see Section 4.2) will be enrolled. Subjects will be consented and enrolled at Visit 1. Pre-procedural transesophageal echocardiography will be performed at the discretion of the investigator. Subjects will be treated with apixaban for ≥21 days prior to ablation; for subjects already being treated with apixaban for ≥21 days, it is not necessary to wait 21 days between Visit 1 and Visit 2. Eligible subjects will be randomized prior to the procedure (Visit 2); randomization may take place on the day of the procedure or up to 3 days prior. Subjects not randomized will be considered screen failures. Apixaban dose will be 5 mg b.i.d.; per product label, however, the dose will be 2.5 mg b.i.d. in subjects with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

It is anticipated that up to 360 subjects may be enrolled in order to evaluate a total of 300 randomized subjects. Subjects will be randomized in a 1:1 ratio to 2 peri-procedural treatment strategies (150 subjects per cohort):

1. Uninterrupted treatment: administer the evening apixaban dose on the day prior to the procedure; administer the morning apixaban dose on the day of the procedure; administer heparin bolus before transseptal puncture to maintain a target activated clotting time [ACT] > 300 seconds; administer the evening apixaban dose after the procedure if there were no peri-procedural complications that necessitate withholding anticoagulation for longer duration.
2. Interrupted treatment: administer the evening apixaban dose on the day prior to the procedure; ***do not*** administer the morning apixaban dose on the day of the procedure; administer heparin bolus before transseptal puncture to maintain a target ACT > 300 seconds; administer the evening apixaban dose after the procedure if there were no peri-procedural complications that necessitate withholding anticoagulation for longer duration.

Randomized subjects will be stratified by site. Apixaban treatment will be continued for at least1 month post procedure, until the end of the study. Study visits will be at screening/enrollment, pre-procedure/ discharge, and at 1 month for follow-up. Subject participation in the study will conclude at the follow-up/end-of-study visit conducted at 1 month post-ablation.

A Study Schema is shown in Section 6.1 and the Schedule of Events in Section 6.2

4.1.2 Retrospective, Warfarin Cohort

In addition, due to diverse definitions of the components of the primary endpoints in previous studies (e.g., clinically significant bleedings), a chart review of 300 warfarin-treated patients who underwent catheter ablation for NVAF on or after September 1, 2013 in the enrolling centers and who have documented follow-up in the medical record for ≥ 30 days post-ablation procedure will be performed to assess the incidence of the adjudicated primary endpoints in the current clinical setting. Patient records for warfarin-treated individuals who meet the applicable inclusion/exclusion criteria and who are matched 1:1 to a subject in the prospective, randomized cohort for age (+/- 5 years), gender and AF type (paroxysmal vs. persistent), will be identified. Sites will document key demographic and outcome variables. This review will be performed in a blinded manner such that site personnel are blinded to the outcome of each retrospective subject during the subject selection process. Only pre-existing data will be collected for the analysis of this cohort.

4.2 Study Population

4.2.1 Inclusion Criteria

Subjects meeting **all** of the following criteria may be included:

For the randomized, prospective cohort:

1. Signed 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 or their legal representatives will indicate that consent by signing and dating the informed consent document in the presence of study personnel.
2. ≥18 years of age.
3. NVAF with planned catheter ablation treatment.
4. Planned anticoagulant treatment for at least 1 month after the index procedure.
5. Subject agrees to all required follow-up procedures and visits.
6. For women of childbearing potential (WOCBP):

- Must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study drug.
- Must not be breastfeeding
- Must agree to follow instructions for method(s) of contraception for the duration of treatment with the study drug apixaban, plus 5 half-lives of apixaban (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion.

7. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with the study drug apixaban plus 5 half-lives of the apixaban (3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion.
8. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as described in this section.

For the retrospective, warfarin cohort:

1. ≥18 years of age, at the time of the historical catheter ablation procedure.
2. NVAF with catheter ablation treatment on or after September 1, 2013 in the enrolling center.
3. Treatment with a strategy of "uninterrupted warfarin" prior to and following catheter ablation (i.e. no peri-procedural bridging with low molecular weight heparin).
4. Medical record includes documentation of follow-up for ≥ 30 days post-ablation, i.e. follow-up visit or phone contact (at the facility or with other medical provider).
5. Baseline characteristics in patient record match 1:1 with a subject in the prospective, randomized cohort within the same study site, based on all of the following criteria:
   - Age (+/– 5 years)
   - Gender
   - AF type (paroxysmal vs. persistent).

4.2.2 Exclusion Criteria

Subjects meeting **any** of the following criteria will be excluded:

For the randomized, prospective cohort:

1. History of significant bleeding diathesis or coagulopathy or inability to accept blood transfusions.

2. Known hypersensitivity or contraindication to heparin or apixaban.
3. Subjects with mechanical prosthetic heart valves.
4. History of cerebrovascular accident or transient ischemic attach (TIA) within the last 6 months.
5. Prior intracranial hemorrhage.
6. End-stage renal failure (creatinine clearance rate <15 mL/minute or on dialysis treatment).
7. Hepatic disease associated with coagulopathy.
8. Current or expected systemic treatment with strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort).
9. Current or expected systemic treatment with dual antiplatelet therapy, other anticoagulants, or fibrinolytics.
10. Planned or expected surgery, or other invasive procedure that would require interruption of anticoagulation within 1 month of the catheter ablation procedure.
11. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
12. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or that could impact the scientific integrity of the trial.
13. Platelet count $\leq$100,000/mm^3.
14. Hemoglobin level <9 g/dL.
15. Any active bleeding.
16. Prisoners or subjects who are involuntarily incarcerated.
17. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

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. See Appendix 1 for complete US prescribing information for apixaban.

For the retrospective, warfarin cohort:

Exclusion criteria 1-15 apply to this study population, applicable at the time of the historical catheter ablation procedure.

4.2.3 Contraception Requirements

The information in this section is applicable to the prospective, randomized cohort subjects only.

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:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- 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 partner. Female 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.

4.2.4 Women of Childbearing Potential

The information in this section is applicable to the prospective, randomized cohort subjects only.

A 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 the age of 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 >40 mIU/mL to confirm menopause.

Note that females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period 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 judgment 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.

4.2.5 Discontinuation of Subjects from Treatment

The information in this section is applicable to the prospective, randomized cohort subjects only.

Subjects MUST discontinue investigational product 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 that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in Section 5.8.3. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

5 TREATMENTS

This section applies to the prospective, randomized cohort subjects only.

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

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.

5.1.1 Identification, Packaging, and Labeling

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance	Storage Conditions (per label)
Apixaban tablet	2.5 mg	Bottles of 60/ marketed label	Yellow, round, biconvex, film-coated tablets with "893" debossed on one side and "2½" on the other side.	Store at 20°C to 25°C (68°F–77°F); excursions permitted between 15°C and 30°C (59°F–86°F)
Apixaban tablet	5 mg	Bottles of 60/ marketed label	Pink, oval-shaped, biconvex, film-coated tablets with "894" debossed on one side and "5" on the other side.	Store at 20°C to 25°C (68°F–77°F); excursions permitted between 15°C and 30°C (59°F–86°F).

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.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity), as described below:

Apixaban film-coated tablets should be stored between 20 °C and 25 °C (68–77 °F), with excursions permitted between 15 °C and 30 °C (59–86 °F).

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

5.2 Drug Ordering and Accountability

5.2.1 Apixaban Orders

The HCRI project manager should be contacted for study drug requirements. Details of drug accountability, ordering, re-supply, and shipment will be provided in the study manual.

5.3 Randomization

Before the catheter ablation procedure, subjects will be randomly assigned in a 1:1 ratio to 1 of 2 peri-procedural treatment strategy cohorts (uninterrupted versus interrupted treatment) via the HCRI InForm database and based on a randomization list provided by HCRI and stratified by site. Randomization may take place on the day of the procedure, prior to time of the subject's morning dose of apixaban, or it may take place up to 3 days prior to the procedure.

5.4 Selection and Timing of Dose for Each Subject

Subjects not already taking apixaban will be treated with the recommended dose of apixaban from at least 21 days prior to the catheter ablation procedure through 1 month post procedure, until the final study visit; however, for subjects already taking apixaban for ≥ 21 days, it will not be necessary to wait for 21-42 days for Visit 2 to occur. The dose of apixaban will be 5 mg b.i.d. administered orally. A dose adjustment to 2.5 mg b.i.d. will be required for subjects with 2 or more of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Before the procedure, subjects will be randomized to receive uninterrupted or interrupted therapy as described below. After the procedure, subjects will receive the same dose of apixaban that they received prior to the procedure, for 1 month.

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, 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 should not be used if a subject has active pathological bleeding. It is not recommended in patients with severe hepatic impairment.

For complete dosing information, see Appendix 1 for the US prescribing information.

5.4.1 Uninterrupted Randomized Arm

Subjects randomized to the uninterrupted treatment arm will receive the apixaban dose in the morning before the procedure. A heparin bolus will be administered before transseptal puncture to maintain a target ACT > 300 seconds. After the procedure, the subject will be administered the evening apixaban dose only if no peri-procedural complications occurred that would necessitate withholding anticoagulation for longer duration. Apixaban treatment will then be continued for at least 1 month post procedure, until the final study visit.

5.4.2 Interrupted Randomized Arm

Subjects randomized to the interrupted treatment cohort will **NOT** receive the apixaban dose in the morning before the procedure. A heparin bolus will be administered before transseptal puncture to maintain a target ACT > 300 seconds. After the procedure, the subject will be administered the evening apixaban dose only if no peri-procedural complications occurred that would necessitate withholding anticoagulation for longer duration. Apixaban treatment will then be continued for at least 1 month post procedure, until the final study visit.

5.4.3 Temporary Discontinuation of Apixaban

Discontinuing anticoagulants, including apixaban, for active bleeding, elective surgery, or invasive procedures, places subjects at an increased risk of thrombosis. Lapses in therapy should be avoided and, if anticoagulation with apixaban must be temporarily discontinued for any reason (with the exception of temporary discontinuation for subjects randomized to the interrupted arm as specified above), therapy should be restarted as soon as possible. Treatment continuation after the last visit of the study is at the discretion of the treating physician.

5.5 Blinding/Unblinding

This is not a blinded study.

5.6 Concomitant Treatments

5.6.1 Prohibited and/or Restricted Treatments

For complete contraindication, interaction, and precaution information, see Appendix 1 for the US prescribing information for apixaban.

5.6.2 Other Restrictions and Precautions

Other than the catheter ablation procedure performed during this study, if possible, apixaban should be discontinued 2 to 3 days prior to elective surgery or invasive procedures. 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 with antiplatelet agents increases the risk of bleeding. In subjects with NVAF 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.

Use apixaban with caution when co-administered with nonsteroidal anti-inflammatory drugs, including aspirin.

For complete contraindication information, see Appendix 1 for the US prescribing information for apixaban.

5.7 Treatment Compliance

Treatment compliance will be determined by subject self-report. If the subject reports that they missed doses of apixaban in the following circumstances, they will be **discontinued** from participation in the study (and classified as screen failures):

1. If the subject reports missing ≥ 1 dose on the day before the procedure.

2. If the subject misses ≥ 4 consecutive doses during the 21 days prior to the catheter ablation *and* there is no transesophageal echocardiography (TEE) planned prior to the catheter ablation.

5.8 Handling Subjects Withdrawn, Lost to Follow-Up, or Removed from the Study

5.8.1 Handling of Subject Withdrawals

Although a subject is not obliged to give his/her reason for withdrawing prematurely, the site PI will make a reasonable effort to obtain the reason while fully respecting the subject's rights. If there is a medical reason for withdrawal, the subject will remain under the supervision of the site PI until in satisfactory health. Reasonable efforts will be made to contact a subject who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

5.8.2 Handling of Subjects Lost to Follow-Up

Every attempt must be made to have all subjects complete the visit schedule. A subject will not be considered lost-to-follow-up unless all efforts to obtain compliance are unsuccessful. Study sites should attempt to contact these subjects in order to maintain study visit compliance and all contact attempts should be documented in both the subject's medical records and on the study electronic case report form (eCRF). At a minimum, the site should make two attempts (at least 3-5 days apart and on both business and non-business hours) to contact the subject by phone and one by certified mail.

5.8.3 Removal of Subjects from the Trial or Study Drug

Subjects will be informed that they are free to withdraw from the study at any time should they so wish without jeopardizing their medical care. The site PI may remove a subject if, in his/her opinion, it is in the best interest of the subject. A subject may be withdrawn from the study for any of the following reasons:

- Deviation/noncompliance with the protocol occurs
- A serious or intolerable adverse event (AE) occurs
- The Sponsor or site PI terminates the study

- Withdrawal of consent - any subject may withdraw his/her consent from the study at any time. The site PI should make a reasonable attempt to document the specific reason why consent is withdrawn.
- The site PI or Sponsor decides that discontinuing the trial or discontinuing the subject is in the subject's best interest
- The subject is lost to follow-up

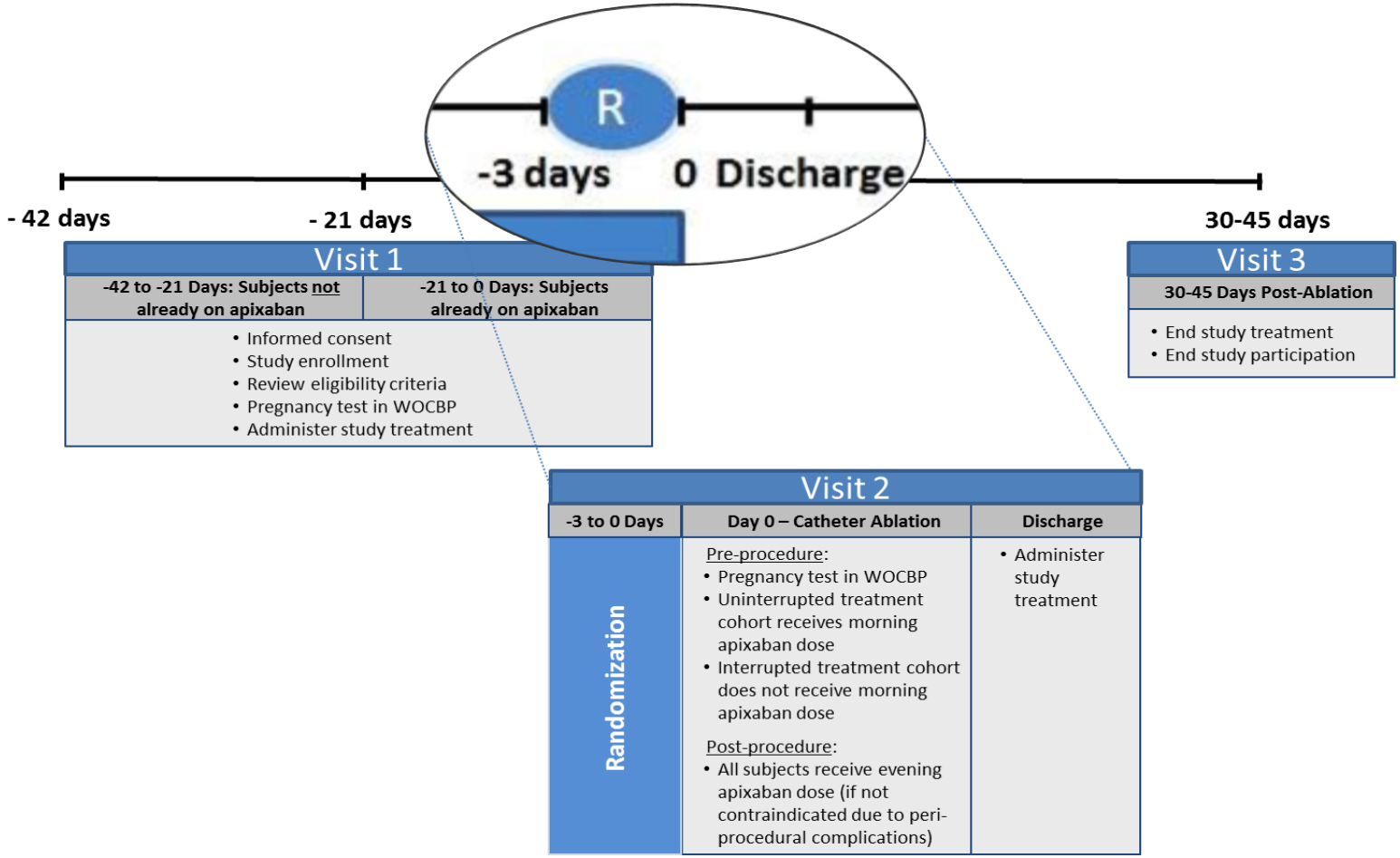
A study completion eCRF, which includes the reason for discontinuation, must be completed for all subjects. If the subject discontinues prematurely, the study completion eCRF should clearly indicate the reason for discontinuation. If the subject discontinues due to an AE, an AE eCRF must be completed. The AE must be followed by medical attention to satisfactory resolution and all trial data related to the subject will be reported.

Every effort will be made to continue clinical and laboratory follow-up in subjects who wish to withdraw from the study treatment (medication or placebo) or in whom the study medication is stopped by the site PI or per individual stopping rules.

6 STUDY ASSESSMENTS AND PROCEDURES

This section applies to the prospective, randomized cohort subjects only.

6.1 Study Schematic



6.2 Time and Events Schedule

Table 1 Schedule of Events for Protocol CV185-373

Evaluation	**Visit 1 Screening/ Enrollment**	**Visit 2 Pre-Procedure and Discharge**			**Visit 3 1-Month Follow-Up/ End of Study[1]**
Study day	0 to 42 Days before procedure[2]	0-3 Days before procedure	Day of procedure, Day 0	Day of discharge	30 to 45 Days after procedure
Informed consent	X				
Screening/eligibility criteria[3]	X[4]		X[4]		
Enrollment	X				
Medical/social history, demographics, baseline characteristics	X				
CHA_2DS_2-VASc	X				
HAS-BLED, $HEMORR_2HAGES$	X				
Physical examination	X		X[5]	X[5]	X[5]
Vital signs	X		X	X	X
Randomization		X			
Clinical laboratory tests[6]	X		X		
Catheter ablation procedure			X[7]		
Administration of study treatment	X		X[8]	X	
Termination of study treatment					X
Study treatment accountability			X		X
Thrombotic events, bleeding (BARC criteria)	X		X	X	X
Adverse events	X		X	X	X
Concomitant medications	X		X	X	X
End of subject participation					X

BARC: Bleeding Academic Research Consortium; CHA_2DS_2VASc: Congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category score; HAS BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol bleeding risk score; $HEMORR_2HAGES$: hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke bleeding risk score.

1. In the event of early study withdrawal or treatment discontinuation, an end-of-study visit should be conducted. The reason for early withdrawal/study drug discontinuation must be documented.
2. Subjects already taking apixaban for ≥ 21 days do not have to wait for the 21-day window for Visit 2 to occur.
3. Screening/eligibility criteria are detailed in section 7.1.
4. Urine or serum pregnancy test will be performed for screening within 24 hours prior to start of study drug and within 24 hours prior to the catheter ablation procedure in WOCBP.
5. Physical examination to assess any clinically significant changes from screening, including neurological examination.
6. Clinical laboratory tests are detailed in Section 6.3.5.
7. Catheter ablation will be performed on the day of Visit 2 (day 0).
8. Subjects randomized to the uninterrupted treatment cohort will receive the morning dose of study treatment pre-procedure. Subjects randomized to the interrupted treatment cohort will not receive the morning dose of study treatment pre-procedure.

6.3 Study Procedures and Evaluations

6.3.1 Informed Consent

Potential study subjects will report to the investigative site for eligibility screening. Before any study-specific procedures are conducted, the nature, purpose, potential risks and benefits, and requirements of the study must be explained to each potential subject, and the potential subject must be given an opportunity to ask questions concerning the study until he or she is satisfied. The nature and purpose of informed consent must also be explained to the potential subjects. All subjects will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time. They will have adequate opportunity to ask the appropriate person of the study staff (i.e., site PI or designee) presenting the study about any aspect of the study. Once the subject is satisfied that he/she is willing to participate in the study, he/she will be asked to sign and date the written ICF. No study procedure is permitted to be performed until the ICF is signed. The PI or designee obtaining informed consent from the subject will also sign the ICF to confirm that consent has been obtained as required. A copy of the signed ICF will be given to the subject. The subject's medical record should contain written documentation indicating that voluntary informed consent was obtained.

6.3.2 Medical History

A detailed medical history will be obtained by the PI or designee during the screening visit (visit 1). This will include information regarding the subject's full history of medical conditions, diagnoses, procedures, treatments, concomitant medications, demographic information, and any other noteworthy medical information, with dates of start and finish. Data on baseline characteristics, including chronic renal insufficiency (%), gastrointestinal bleeding, and smoking will also be collected. Any updates to medical history information that the PI or designee becomes aware of will be captured throughout the study.

6.3.3 Physical Examination

The PI or a medically qualified designee will perform the physical examinations at the time points indicated in the schedule of events (SOE; Section 6.1). A complete physical examination will include assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, targeted neurological examination, and general appearance. The physical examination will not include a pelvic, breast, or rectal examination.

Weight (in kg; assessed in ordinary indoor clothing with shoes off) will be recorded according at the time points indicated in the SOE. Height (in cm) will be recorded at screening (visit 1) only.

Body mass index (BMI) will be calculated at screening (visit 1) only and is defined as the subject's weight in kilograms divided by the square of the subject's height in meters (kg/m^2).

If any clinically significant change from screening (visit 1) is noted, it will be reported as an adverse event and followed up to resolution or upon reaching a stable end point.

6.3.4 Vital Signs

Evaluation of vital signs will be performed by qualified site personnel after the subject has been seated for 5 minutes, and will include a measurement of systolic and diastolic blood pressure, pulse rate, oral temperature, and respiratory rate. Vital sign measurements will be obtained at all visits (visits 1, 2, and 3), as indicated in the SOE. Blood pressure should be taken on the same arm throughout the study and will be obtained using a completely automated device consisting of an inflatable cuff and an oscillatory detection system. Manual blood pressure readings may be obtained in the event of instrument malfunction. Body temperature will be measured with an oral thermometer.

If the PI or medically qualified sub-investigator determines that clinically significant changes have occurred in any vital sign measurement, that measurement will be captured as an adverse event and repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

6.3.5 Clinical Laboratory Tests

6.3.5.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. All clinical laboratory assessments will be performed by a local clinical laboratory accredited by the College of American Pathologists or a certificate of compliance issued by the Center for Medicare & Medicaid Services, Clinical Laboratory Improvement Amendments. The laboratory assessments will include routine and screening laboratory tests. See Section 6.2 for the SOE. Système International (SI) units will be used for all assessments.

Routine safety laboratory panels will include:

- Hematology: white blood cell count, hemoglobin, hematocrit, and platelet count.
- Serum chemistry: glucose, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate, alkaline phosphatase (AP), aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin.

Any abnormal hematology, serum chemistry, or test result deemed clinically significant by the PI or medically qualified sub-investigator will be reported as an adverse event and repeated as appropriate as standard of care, including test results obtained on the final study day. For any test

abnormality deemed erroneous or clinically significant, repeat analysis will be performed as per standard of care until resolution, or until the PI or medically qualified sub-investigator determines that resolution of the laboratory abnormality is not expected.

6.3.5.2 Sample Collection, Storage, and Shipping

All blood sampling will be by individual venipuncture or with the use of an in-dwelling venous catheter. Blood and urine sample collection and processing procedures will be outlined in a separate reference manual to be provided to the site.

6.3.6 Safety Assessments

The PI is ultimately responsible for assessing and reporting all AEs as outlined in the protocol. The assessment of AEs may be delegated to a medically qualified sub-investigator trained in study protocol who is listed on the Food and Drug Administration (FDA) Form 1572 or equivalent document, and on the Delegation of Authority form.

AEs should be volunteered by the subject; solicited from subjects using a standard statement; or examination of the subject at a clinic visit, or observations of clinically significant laboratory values or special exam abnormal values. AEs will not be solicited by use of a specific list of anticipated events.

All AEs are to be assessed and recorded in a timely manner and followed to resolution or until the investigator determines that there is not an anticipated resolution. Each AE is to be documented with reference to severity, date of occurrence, duration, treatment, and outcome. Each AE is also to be classified as being non-serious or serious (as defined in Section 8.2). In addition, the PI or delegated medically qualified sub-investigator must assess whether or not the AE is drug-related. Changes in severity and resolution dates should be documented as separate events.

See Section 8 for complete information regarding AEs.

6.3.7 Efficacy and Safety Assessments

Thrombotic events will be assessed and are defined as a composite of non-hemorrhagic stroke and systemic thromboembolic events.

Clinically significant bleeding will be assessed and is defined as bleeding meeting BARC criteria type 2 or higher. BARC definitions for bleeding are shown in Appendix 2.

7 STUDY ACTIVITIES

This section applies to the prospective, randomized cohort subjects only.

7.1 Visit 1: Screening and Enrollment: 0 to 42 Days Prior to the Catheter Ablation Procedure

Visit 1 (screening/enrollment) will occur 0 to 42 days prior to the catheter ablation procedure. For subjects not already taking apixaban, Visit 1 will occur 21-42 days prior to the procedure. For subjects already taking apixaban for ≥ 21 days, it will not be necessary to wait for 21-42 days for Visit 2 to occur. The following study evaluations and procedures will be performed at this visit:

- The signed informed consent will be obtained before any screening or other study related procedures are initiated.
- Assignment of a subject number. When a subject signs the ICF, she/he will be assigned a unique subject number in numerical sequence, which will be used for the duration of the study. The subject number will be recorded in the source document and case report form.
- Review of the inclusion and exclusion criteria.
- Recording of the subject's demographic information, baseline characteristics, and comprehensive medical history.
- Physical examination, including targeted neurological examination.
- Vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, oral temperature) after a minimum 5-minute rest in the supine position.
- Administration of pre-procedure treatment
- CHA_2DS_2VASc (Congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category score)
- HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol bleeding risk score)
- $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke bleeding risk score)
- Clinical laboratory tests (refer to Section 6.3.5)
- Urine or serum pregnancy test will be performed for screening within 24 hours prior to start of study drug in WOCBP.
- Dispensation and administration of study treatment, if applicable.
- Evaluation for clinically significant bleeding and thrombotic events.

- Recording of AEs and concomitant medications.

7.2 Visit 2: The Day Prior to the Procedure, the Day of the Procedure (Day 0), and the Day of Discharge

Randomization to 1 of 2 peri-procedural treatment strategies, uninterrupted treatment or interrupted treatment, will occur prior to the ablation procedure. It may take place on the day of the procedure, prior to time of the subject's morning dose of apixaban, or up to 3 days prior to the procedure, but no visit is required for this. Visit 1 and randomization may take place on the same day for subjects already taking apixaban for ≥ 21 days.

Visit 2 will occur on the day of the ablation procedure (day 0) and the day of discharge from the hospital.

Pre-procedure study evaluations and procedures will occur on the day of the catheter ablation and will include:

- Brief physical examination to assess any clinically significant changes from screening, including targeted neurological examination.
- Vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, oral temperature) after a minimum 5-minute rest in the supine position.
- Routine clinical laboratory tests, including hematology and serum chemistry (using a venous blood sample).
- Urine or serum pregnancy test will be performed within 24 hours of catheter ablation procedure in WOCBP.
- Subjects randomized to the uninterrupted treatment cohort will receive the morning dose of study treatment pre-procedure. Subjects randomized to the interrupted treatment cohort will ***not*** receive the morning dose of study treatment pre-procedure.
- Evaluation for clinically significant bleeding and thrombotic events.
- Recording of AEs and any changes to concomitant medications, including dose or regimen changes.
- Drug accountability.

Post-procedure study evaluations and procedures will include:

- All subjects will receive the evening apixaban dose after the procedure if there were no peri-procedural complications that necessitate withholding anticoagulation for longer duration

- Evaluation for clinically significant bleeding and thrombotic events.
- Recording of AEs and any changes to concomitant medications, including dose or regimen changes.
- For all subjects, the twice daily apixaban dose will be resumed the day after the catheter ablation procedure while the subject remains in the hospital.

Discharge study evaluations and procedures will occur on the day the subject is to be discharged from the hospital and will include:

- Brief physical examination to assess any clinically significant changes from screening, including targeted neurological examination.
- Vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, oral temperature) after a minimum 5-minute rest in the supine position.
- Evaluation for clinically significant bleeding and thrombotic events.
- Recording of AEs and any changes to concomitant medications, including dose or regimen changes.
- Drug accountability.
- If not already occurring, dispensation and administration of study treatment.

7.3 Visit 3: 1-Month Follow-Up/End of Study: Day 30-45

Visit 3 (1-month follow-up/end of study) will occur 1 month after the ablation procedure (day 30 to 45). The following study evaluations and procedures will be performed at this visit:

- Brief physical examination to assess any clinically significant changes from screening.
- Vital sign measurements (systolic and diastolic blood pressure, pulse, respiration rate, oral temperature) after a minimum 5-minute rest in the supine position.
- Termination of study treatment.
- Study treatment accountability.
- Evaluation for clinically significant bleeding and thrombotic events.
- Recording of AEs and any changes to concomitant medications, including dose or regimen changes.
- End of subject participation.

8 ADVERSE EVENTS

This section applies to the prospective, randomized cohort subjects only.

8.1 Definition and Causality

An 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 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.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. Adverse events may include:

- Objective signs observed by the site PI or study personnel.
- Subjective or objective signs/symptoms.
- Concomitant disease or accidents.
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study.

Pre-existing conditions that worsen in severity or frequency or have new signs/symptoms associated with them.

8.2 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.
  - Potential drug-induced liver injury (DILI) is also considered an important medical event. See the DILI section below for a definition of a potential DILI event.

Suspected transmission of an infectious agent (e.g., 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.

SAEs also include events that are medically significant in the site PI's judgment, including medically significant laboratory abnormalities, such as those that warrant stopping study treatment for individual subjects.

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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.2.1 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 blood draw).

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 Form should be completed for any event in which 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 HCRI within 24 hours. SAEs must be recorded on the SAE Report Form, pregnancies on a Pregnancy Surveillance Form. The site PI or designated personnel should enter the SAEs into the clinical database. If in the unlikely event the database is not functioning, the site personnel should email or fax the SAE information to HCRI.

SAE Fax Number: 1-617-307-5626

SAE Email Address: AXA14@srcdocs.hcri.net

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 HCRI (or designee) using the same procedure used for transmitting the initial SAE report.

The site PI must also promptly inform the governing IRB/EC of the SAE per the governing IRB/EC's requirements. All SAEs should be followed to resolution or stabilization.

8.2.2 SAE Reconciliation

HCRI Clinical Review and Safety in collaboration with the HCRI Data Management (DM) team will reconcile the clinical and safety databases according to the SAE Reconciliation Plan. The SAE Reconciliation Plan details the parameters to be reconciled, data format, frequency and timing and designated responsibilities for reconciliation. Updates will be made to the safety database if discrepancies are found during reconciliation. A follow-up report will be submitted to applicable reportable events as a follow-up Med Watch report following completion of SAE reconciliation. SAE reconciliation final approval will occur after all discrepancies are resolved and the designated representatives agree that the clinical trial and safety databases are reconciled.

8.3 Non-Serious Events

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

8.3.1 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of NSAE information should begin after the subject has signed the informed consent form.

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

8.4 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 (e.g., use the term *anemia* rather than *low hemoglobin value*).

Other findings related to abnormal laboratory values, ECGs, vital signs, etc., that are not considered clinically significant, are not to be recorded on the AE reporting page; they should instead be entered in the relevant eCRF page.

8.5 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 (apixaban) exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The investigator must immediately notify HCRI of this event via the Pregnancy Surveillance Form within 24 hours (to be faxed or emailed to HCRI at 1-617-307-5626 or at AXA14@srcdocs.hcri.net) and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, if 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 HCRI. 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 (e.g., X-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

8.6 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.

8.7 Potential Drug-Induced Liver Injury

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, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation >3 times upper limit of normal (ULN).

AND

2. Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated serum AP)

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.8 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 nonserious or serious AE, as appropriate, and reported accordingly.

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9 STATISTICAL CONSIDERATIONS

9.1 General Statistical Analysis Plan

This study will examine results in two groups of randomized, prospective subjects, and one group of retrospective, warfarin subjects. For the randomized groups, subjects undergoing catheter ablation for NVAF will be enrolled. These subjects will be randomized 1:1 to two peri-procedural treatment strategies: uninterrupted apixaban or interrupted apixaban. Randomization of subjects will be stratified by site. The primary safety endpoint is the incidence of the clinically significant bleeding from time of randomization through 1 month post-catheter ablation. The primary efficacy endpoint is the incidence of thrombotic events assessed from the time of randomization through 1 month post–catheter ablation. The primary analyses will compare the two groups of randomized subjects on the incidence rate of these endpoints. Secondary analyses will compare all randomized subjects (both arms combined) to the retrospective warfarin control group on the incidence rate of these endpoints. The control group is comprised of patient records from warfarin-treated individuals (retrospective) who underwent ablation for NVAF on or after September 1, 2013 in the enrolling centers, and who are matched to the prospective (apixaban) subjects by age (+/-5 years), gender, and type of AF (paroxysmal vs. persistent). For the retrospective warfarin group, the process of selecting subjects for matching will be performed by site personnel, blinded to the matched subject's outcome.

9.2 Sample Size Determination

Given the nature of the pilot study, it is not powered for the primary analyses of comparing randomized treatments. The sample size however is based on an evaluation of anticipated event rates as compared with current literature as described further below. While not definitively powered to detect differences in the randomized groups, this study should provide useful information on this patient population.

For the primary analysis of the comparison of the interrupted versus uninterrupted apixaban treatment strategies, the primary efficacy and safety endpoint rates and the exact 2-sided 95% confidence intervals of the primary efficacy and safety endpoints for each apixaban group (and for both apixaban groups combined) and a 2-sided 95% confidence interval of the risk difference between the apixaban groups (calculated using the Wilson method) will be displayed for apixaban-treated subjects. It is noted that this is a pilot study and this analysis will have limited power.

The event rate for clinically significant bleeding from the literature is difficult to obtain with the protocol specified definition. Recent registries show rates of major bleeding of approximately 2%, and minor bleeding of 6-12%. Minor bleeding has not been consistently defined and is difficult to compare across trials. To be conservative, we adopted an event rate of 4% for warfarin. Although in the ARISTOTLE trial comparing warfarin and apixaban in patients with AF (not undergoing ablation) the bleeding rate was 20-30% lower with apixaban, we have conservatively assumed that the rate will be the same. As such, the assumed rate of clinically significant bleeding for apixaban is 4.0%.

For the primary analyses on the primary safety endpoint, assuming an *evaluable* sample size of 150 per randomized group and an event rate of 4.0% for each of the interrupted and uninterrupted apixaban groups, the width of the confidence interval for the risk difference between randomized groups will be 10% (i.e., the 95% CI of the risk difference will be -5% to +5%).

In addition, the secondary analysis of the efficacy and safety endpoints will compare the rates (from randomization to 1 month post-ablation) of clinically significant bleeding events, and of thrombotic events observed in the apixaban prospective randomized cohort, compared to that observed in the matched, retrospective warfarin cohort who meet inclusion/exclusion criteria. These analyses will be performed on the evaluable population.

For the secondary analyses of comparing apixaban (both interrupted and uninterrupted combined) to warfarin, assuming an evaluable sample size of 300 patients for each of apixaban and warfarin cohorts and a clinically significant bleeding event rate of 4% for each of these two

groups, the width of the confidence interval for the risk difference between groups will be 6.7%. (i.e., the 95% CI of the risk difference to be -3.35% to +3.35%).

Sample size justification

A tertiary but important current aim of the study is to assess the combined thrombotic/bleeding rate for both groups combined via an approach using a comparison to a literature-derived boundary. The literature-based boundary is derived from the warfarin event rates reported in studies assessing novel oral anticoagulants versus warfarin in the setting of ablation, and in which 3-month rates were reported. This strategy ensures the boundary is reflective of current standards of care.

We searched PUBMED for the following search criteria: "(dabigatran AND ablation) OR (rivaroxaban AND ablation) OR (apixaban AND ablation) OR (novel oral anticoagulants AND ablation)." The search yielded 78 titles, of which 12 full-text articles were retrieved for in-depth review. The following 5 studies were identified:

Study	Warfarin Group Size	Clinically Significant Bleeding and Thrombotic Events*
Kaseno *et al.*[1]	101	13 (12.9%)
Bassiouny *et al.*[2]	623	24 (3.9%)
Kaiser *et al.*[3]	135	12 (8.9%)
Kim *et al.*[4]	572	31 (5.4%)
Yamaji *et al.*[5]	203	7 (3.4%)

* Includes thromboembolic events, major clinically significant bleeding events, and minor bleeding events.

A meta-analytic rate of the composite of clinically significant bleeding and thrombotic events is calculated to be 5.5% (± 1.1%) from a random effects meta-analysis (random effects meta-analysis was used due to significant heterogeneity among studies).

Because most events will occur early after the index event, and to compare rates at one month (rather than 3 months in the literature), we will use a composite event rate of 5.0% for the apixaban group. Other recent studies, having differing definitions of major bleeding, have event rates ranging from 3% to 12%.[6-8] As such, a conservative 5% rate for the composite seems reasonable.

An analysis of the two groups of apixaban combined (300 subjects) will be used in this tertiary analysis to assess if the upper bound of the 1-sided 95% confidence interval of the 1-month rate

of clinically significant bleeding and thrombotic events (and additionally of the composite of major bleeding and thrombotic events) falls below a boundary of 8.7%. Specifically, this analysis will assess whether apixaban (in both randomized groups combined) in the setting of catheter ablation can meet a boundary of 8.7%, which is an absolute increase of 3.7% over the expected rate of 5.0% obtained from the meta-analysis. In other words, this analysis will test the following null and alternative hypotheses:

$$H_0: \pi \geq 0.087 \text{ (or } 8.7\%)$$

$$H_1: \pi < 0.087 \text{ (or } 8.7\%)$$

where π is the true (unknown) apixaban endpoint rate.

The following assumptions were used for the sample size calculations:

- Assessment is that the incidence of a composite of clinically significant bleeding and thrombotic events (and composite of major bleeding and thrombotic events) in the setting of apixaban treatment (interrupted and uninterrupted combined) peri- and post-ablation for NVAF meets the literature-based boundary using a 1-sided exact test based on the binomial distribution.
- The true apixaban event rate at 1 month is assumed to be 5.0%.
- Type I error (α) = 0.05 (1-sided).
- Power of 80%.

A sample size of 300 apixaban subjects in the prospective, randomized cohort provides 80% power to meet this boundary, with the upper bound of the 1-sided 95% confidence interval of the event rate in the study cohort not exceeding 8.7%. It is estimated that up to 360 subjects will be enrolled to randomize 300 subjects.

9.3 Populations for Analyses

Intention-to-treat (ITT): All subjects randomized to either interrupted or uninterrupted apixaban.

Evaluable: The subset of the ITT population who experienced a primary endpoint prior to 1 month (30 days) post–index procedure or who were followed through 1 month (30 days minus an allowable 3-day visit window) post–index procedure. This is the primary analysis population for the primary endpoint and for efficacy in general. Subjects are analyzed under the treatment to which they were randomized.

Safety: All subjects receiving randomized study treatment. This is the primary analysis population for safety. Subjects are analyzed under the treatment received.

Historical Control: The retrospective cohort of patient records from 300 warfarin-treated individuals who underwent catheter ablation for NVAF in the enrolling centers on or after September 1, 2013 and who were matched for age, gender and type of AF (paroxysmal vs. persistent) to the 300 prospective apixaban patients.

9.4 Endpoints

9.4.1 Definitions

Thrombotic events are defined as a composite of non-hemorrhagic stroke and systemic thromboembolic events.

Clinically significant bleeding is defined as bleeding meeting Bleeding Academic Research Consortium (BARC) criteria type 2 or higher. See Appendix 2 for BARC definitions.

Major bleeding is defined as bleeding meeting BARC criteria type 3 or higher.

9.4.2 Primary Endpoints

1. The primary safety endpoint is the incidence of clinically significant bleeding assessed from the time of randomization through 1 month post–catheter ablation.
2. The primary efficacy endpoint is the incidence of a thrombotic events assessed from the time of randomization through 1 month post–catheter ablation.

9.4.3 Secondary Endpoints

Major Secondary Endpoints

1. Incidence of a composite of major bleeding and thrombotic events assessed from the time of randomization and from the time of enrollment through 1 month post–catheter ablation.
2. Incidence of a composite of clinically significant bleeding and thrombotic events assessed from the time of randomization and from the time of enrollment through 1 month post– catheter ablation.

Additional Secondary Endpoints

The following additional secondary endpoints will be assessed:

1. Clinically significant bleeding, major bleeding, and thrombotic events, and the composite of both (clinically significant bleeding and thrombotic events; major bleeding and thrombotic events) assessed separately in-hospital, and from randomization and from enrollment through 1 month post–catheter ablation.
2. TIAs or non-hemorrhagic strokes from the time of enrollment and from the time of randomization through 1 month post–catheter ablation.
3. Incidence of death and cardiovascular death from the time of enrollment and from the time of randomization through 1 month post–catheter ablation.

9.5 Analyses

9.5.1 Demographics and Baseline Characteristics

Descriptive statistics of demographic and baseline characteristics will be presented for interrupted apixaban, uninterrupted apixaban, and both apixaban groups combined. Similar descriptive statistics and analyses will be presented for the retrospective warfarin group. Groups (apixaban uninterrupted versus interrupted; apixaban versus warfarin) will be compared on baseline variables using 2-sample t-test for continuous variables and Fisher's exact test for categorical variables.

9.5.2 Efficacy Analyses

The following analyses will be performed on the ITT population and the evaluable population. The analyses on the evaluable population are considered the primary analyses.

9.5.2.1 Primary Efficacy Analyses

For the primary analysis of the comparison of the interrupted versus uninterrupted apixaban treatment strategies, the primary efficacy endpoint rates and the exact 2-sided 95% confidence intervals of the primary endpoint for each apixaban group (and for both apixaban groups combined) and a 2-sided 95% confidence interval of the risk difference between the groups (calculated using the Wilson method) will be presented for apixaban-treated subjects. It is noted that this is a pilot study and this analysis will have limited power.

For the ITT analysis set, there may be missing data on the primary efficacy endpoint due to premature withdrawals prior to 1 month post–index procedure. As a supportive analysis to assess the sensitivity of results to missing data, analyses on the ITT population will incorporate the following approach: Kaplan-Meier rate estimates and 2-sided 95% confidence intervals of the Kaplan-Meier estimates and of the difference between Kaplan-Meier estimates will be presented for the same apixaban groupings. All ITT subjects will be included in the calculation of the

Kaplan-Meier rates; subjects not experiencing the event will be censored at the end of the 1-month follow-up or time of their premature withdrawal, whichever is earlier.

9.5.2.2 Major Secondary Efficacy Analyses

The two major secondary endpoints will be analyzed in a similar manner as the primary efficacy endpoints for the evaluable and ITT analysis sets.

9.5.2.3 Additional Secondary Analyses

The above-mentioned additional secondary endpoints will be assessed and analyzed in a similar manner as the primary and major secondary efficacy endpoints (however, Kaplan-Meier estimates will not be calculated for in-hospital endpoints, and subjects included in the calculation of in-hospital rates do not need to have 1 month of follow-up).

9.5.3 Safety Analyses

Analyses will be carried out in a similar manner as for the primary efficacy endpoint.

The following additional safety analyses will be carried out on the safety population:

The number and percentage of subjects with treatment emergent adverse events (TEAEs) will be presented by MedDRA system organ class and preferred term for each apixaban group (uninterrupted and interrupted) and both apixaban groups combined. A TEAE is defined as an AE starting or worsening in severity on or after start of study treatment. These analyses will be repeated for serious TEAEs and for TEAEs leading to premature discontinuation from the study.

For each apixaban group and both groups combined, descriptive statistics (sample size, median, mean, minimum, maximum) of vital signs and of the change from baseline in vital signs will be presented at each visit.

9.5.4 Other Analyses

1. As a tertiary analysis, the combined thrombotic/bleeding rate for both apixaban groups combined will be compared to a rate derived from the literature. Based on the above-mentioned meta-analysis, the expectation for the true combined thrombotic/bleeding endpoint rate at 1 month is 5.0% for apixaban. However, because strict equality cannot be assessed statistically, this study will assess if the 1-month rate of clinically significant bleeding and thrombotic events (and additionally of the composite of major bleeding and thrombotic events) falls below 8.7% when both treatment arms are combined. Specifically, this tertiary analysis will assess the ability of apixaban in the setting of catheter ablation to meet a literature-based boundary of 8.7%, which is

an absolute increase of 3.7% over the expected rate of 5.0% obtained from the meta-analysis. In other words, this analysis will test the following null and alternative hypotheses:

$$H0: \pi \geq 0.087 \text{ (or } 8.7\%)$$

$$H1: \pi < 0.087 \text{ (or } 8.7\%)$$

where π is the true (unknown) apixaban endpoint rate.

The null hypotheses will be tested using all evaluable apixaban subjects (uninterrupted and interrupted groups combined) at a 1-sided 0.05 level of significance using an exact test based on the binomial distribution. In addition, a 1-sided exact 95% confidence interval of the endpoint rate will be presented and the upper bound will be compared to 8.7%. For completeness, a 2-sided exact 90% confidence interval will also be presented. Note that, prior to carrying out this analysis, the comparability between apixaban groups on this thrombotic/bleeding endpoint will be assessed using a 2-sided 95% Wilson confidence interval. If the confidence interval does not contain 0 and if the difference between apixaban groups is considered clinically different, the above analyses may be repeated for each of the uninterrupted and interrupted apixaban groups, separately.

2. To assess consistency of sites with respect to the primary efficacy and safety endpoint rates, logistic regression will be used to compare sites with respect to the primary endpoints rates for the evaluable population. A 0.15 level of significance will be used to determine if a significant site effect exists. A *P* value <0.15 will not necessarily preclude the sites from being pooled for the final analysis, but will require further inspection (e.g., endpoint results by site) to assess if there is a concern about lack of site poolability. In addition, logistic regression will be used to assess consistency of the interrupted vs. uninterrupted apixaban groups across sites, using a logistic regression model with effects for treatment type (interrupted or uninterrupted), site and the treatment type-by-site interaction. The interaction term will be assessed using a 0.15 level of significance.

3. The rates and 2-sided exact 95% confidence intervals of the primary and major secondary endpoints will be presented by apixaban group and for both apixaban groups combined within the following major subgroups:

    a. Age (<80 and ≥80 years).

    b. CHA_2DS_2-VASc (Congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category) score (< median, ≥ median).

    c. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) and

HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke) bleeding risk scores (< median, ≥ median).

d. Baseline antiplatelet therapy vs. no antiplatelet therapy.

e. Baseline anticoagulation therapy (subjects who are anticoagulation-naïve versus subjects on vitamin K antagonists versus subjects on novel oral anticoagulants).

f. Subjects with ≥2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

g. Apixaban dose.

The purpose of this analysis is to assess consistency of primary and major secondary endpoint rates across the various subgroups

.

9.5.5 Addition Analysis: Comparing Prospective Apixaban with Retrospective Warfarin Cohorts

The rate of the primary endpoint in apixaban subjects (uninterrupted and interrupted groups combined) will be compared with a retrospectively-matched warfarin control group. The control group is comprised of patient records from warfarin-treated individuals (retrospective) who meet inclusion/exclusion criteria, including having undergone ablation for NVAF in the enrolling centers on or after September 1, 2013, who have documented follow-up in the medical record for ≥ 30 days post-ablation procedure, and who meet the other inclusion/exclusion criteria including matched for age, gender and type of AF (paroxysmal vs. persistent). For the warfarin group, retrospective chart review will be performed to assess the incidence of the primary endpoint.

This analysis will compare the 1-month rate of clinically significant bleeding and thrombotic events between the two groups in a similar manner as was used to compare apixaban groups.

10 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) is made up of electrophysiology and non-electrophysiology cardiologists and other clinical experts as required who are not participants in the study. The CEC is charged with the adjudication of pre-specified clinical endpoint events.

At the onset of the trial, the CEC will establish specific criteria used for the categorization of clinical endpoint events, explicit rules outlining the minimum amount of data required for adjudication of each event, and the algorithm followed in order to classify a study endpoint related clinical event. All members of the CEC will remain blinded to the treatment assignment

(for subjects in the prospective, randomized cohort) in their review and adjudication of all endpoint events. The CEC will meet regularly to review and adjudicate clinical endpoint events for which the required minimum data are available. The procedures by which the CEC will operate will be documented in a separate manual.

11 STUDY MANAGEMENT

11.1 Regulatory Documentation

Prior to the start of the study, the following documents must be prepared:

- A completed and signed Form FDA 1572. If during the course of the study any changes occur that are not reflected on the 1572, a new 1572 form must be completed and returned to Sponsor/HCRI for submission to the FDA.
- Current signed curriculum vitae and medical licenses (within 2 years) for the site PI and all sub-investigators listed on the 1572.
- A copy of the original approval for conducting the study by the IRB/EC. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB/EC policy.
- A copy of the IRB/EC approved informed consent form.
- IRB/EC member list and DHHS General Assurance Number (if IRB/EC has an Assurance number).
- Signed Financial Disclosure Form for all personnel listed on the 1572 with a statement of non-voting by study staff.
- The protocol signature page signed and dated by the site PI.

11.2 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, HCRI. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB(s)/IEC(s) of an amendment except when 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.

- HCRI
- 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 HCRI.

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

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

11.2.1 Protocol Deviations

A protocol deviation is defined as any instance during the conduct of the study in which the site PI or other site personnel changed or failed to adhere to the study design or procedures specified by the protocol. Examples of protocol deviations may include: a) enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in the protocol; b) failure to obtain a key safety procedure or lab test; or c) enrollment of a patient during a lapse in IRB/EC approval of the study. Each Investigator shall conduct this clinical study in accordance with this clinical protocol, FDA regulations, Good Clinical Practice, and any conditions of approval imposed by their IRB/EC. Failure to comply with and/or inability to meet FDA regulations may jeopardize further participation of the Investigator or Investigative Center in this and future clinical studies.

All relevant protocol deviations should be submitted by the site on the applicable eCRF, and will be reviewed and assessed for their impact on subject safety by the HCRI.

Major Deviations are defined as any unapproved change in the study procedures or study design that are within the site Investigator's control that may adversely affect the subject's rights, safety or well-being, or the accuracy and reliability of the study data.

Minor Deviations are defined as any unapproved change in the study procedures that are within the site Investigator's control that do not have an impact on the subject's rights, safety or well-being, or the accuracy and reliability of the study data.

Investigators are required to notify HCRI in writing before initiating any deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency (in cases of medical emergency, HCRI should be notified within 24 hours of the occurrence of the deviation). Prior notification is generally not expected in situations where unforeseen circumstances are beyond the PI's control (e.g., subject did not respond to scheduled follow-up, blood sample lost by laboratory, etc.), however, the event is still considered a deviation.

11.3 Monitoring

11.3.1 Initiation of Study Sites

Prior to subject enrollment, a remote study initiation visit will be conducted at each investigational site to ensure the following: IRB/EC approval has been obtained and documented prior to subject screening; the Investigators and study personnel are appropriately trained and clearly understand the study; and the Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

11.3.2 Visits

Periodic remote monitoring visits will be performed in accordance with the approved monitoring plan throughout the clinical study to ensure that the investigator's obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will ensure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to HCRI and the IRB/EC, drug and drug inventory are controlled, and the site PI is executing all agreed-upon activities.

The site will receive notification prior to each remote monitoring visit during the course of the study. The site PI and/or Sub-Investigator and other appropriately trained study staff are expected to be available during the visit.

HCRI, BMS, or their designees retain the right to remove either the PI or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements. HCRI or its designee will perform the monitoring responsibilities according to its standard operating procedures.

The progress of the study will be monitored by:

- Remote monitoring of data.

- Frequent telephone or email communications between the PI, site staff, and assigned study site monitors.

11.3.3 Study Close-Out

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits, all data have been entered into the EDC system, all queries have been resolved, and final electronic signatures have been obtained), a study closeout visit will be conducted. All unused study drugs, and any unused study materials and equipment will be collected and returned to BMS for reconciliation. The study monitor will ensure that the PI's regulatory files are current and complete, and that all outstanding issues from previous visits have been resolved. Other issues that will be discussed with site personnel at this visit include retention of study files, possibility of site audits, publication policy, and that the site PI must notify the site's IRB/EC regarding study closure.

11.4 On-Site Inspection and Audits

The FDA may request access to all study records for inspection and copying. A representative of HCRI or BMS also may use similar auditing procedures. The site PI must agree to permit the FDA, the governing IRB/EC, BMS and HCRI access to all study records and original subject records for auditing purposes and provide support for these actions. The site PI will be informed in advance of this visit.

11.5 Records Retention

11.5.1 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 the sponsor/HCRI, whichever is longer.

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

11.5.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the sponsor)is maintained at each study site where study drug and non-investigational 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 identification number or batch number.
- Amount dispensed to each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted).
- Amount destroyed at study site, if applicable.
- Amount returned to HCRI/the sponsor.
- Retain samples for bioavailability/bioequivalence, if applicable.
- Dates and initials of person responsible for investigational product dispensing/accountability, as per the Delegation of Authority Form.

11.6 Destruction of Investigational Product

If the study drugs are to be destroyed onsite, 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.

11.7 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by HCRI in strict confidence and to request similar confidentiality from his/her staff and the IRB/EC. Study documents provided by HCRI (protocols, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by and HCRI to the investigator may not be disclosed to others without direct written authorization from HCRI, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

12 GLOSSARY OF TERMS

Term	Definition
Expedited safety report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure), or that could be associated with the study procedures.

Term	Definition
Prospective, randomized cohort	Prospectively enrolled subjects who are randomized to uninterrupted vs. interrupted apixaban.
Retrospective, warfarin cohort	Patient records will be identified via chart review and pre-existing data will be collected on these individuals who had catheter ablation for NVAF and were treated with warfarin (to be compared with prospective cohort).

13 LIST OF ABBREVIATIONS

ACT	Activated clotting time
AE	Adverse event
AF	Atrial fibrillation
ALT	Alanine transaminase
AP	Alkaline phosphatase
AST	Aspartate transaminase
BARC	Bleeding Academic Research Consortium
b.i.d.	Twice daily
BMI	Body mass index
BMS	Bristol-Myers Squibb
BUN	Blood urea nitrogen
C	Celsius
CEC	Clinical events committee
CFR	Code of Federal Regulations
CHA_2DS_2-VASc	Congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category (score)
cm	Centimeter
CYP3A4	Cytochrome P450 3A4
DILI	Drug-induced liver injury
dL	Deciliter
DM	Data Management
eCRF	Electronic case report form
F	Fahrenheit
FDA	Food and Drug Administration

FSH	Follicle-stimulating hormone
FXa	Factor Xa
g	Gram
GCP	Good Clinical Practice
HAS-BLED	Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol (score)
HCG	Human chorionic gonadotropin
HCRI	Harvard Clinical Research Institute
HEMORR$_2$HAGES	Hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, re-bleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke (score)
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
kg	Kilogram
L	Liter
mg	Milligram
mL	Milliliter
mm	Millimeter
µmol	Micromole
NOAC	Novel oral anticoagulant
NSAE	Nonserious adverse event
NVAF	Nonvalvular atrial fibrillation
PI	Principal investigator
SAE	Serious adverse event
SI	Système International
SOE	Schedule of events
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack

ULN	Upper limit of normal
US	United States
WOCBP	Woman/women of child-bearing potential

Appendix 1 US Prescribing Information for Apixaban

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets for oral use

Initial U.S. Approval: 2012

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.5, 5.1, 14.1)

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.3)

RECENT MAJOR CHANGES

Boxed Warning	8/2014
Indications and Usage (1.2)	3/2014
Indications and Usage (1.3, 1.4, 1.5)	8/2014
Dosage and Administration (2.1)	8/2014
Dosage and Administration (2.8)	3/2014
Warnings and Precautions (5.1)	8/2014
Warnings and Precautions (5.3)	3/2014
Warnings and Precautions (5.5)	8/2014

INDICATIONS AND USAGE

ELIQUIS is a factor Xa inhibitor anticoagulant 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 to pulmonary 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)

DOSAGE AND ADMINISTRATION

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.2)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 2.5 mg and 5 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (apixaban) (4)

WARNINGS AND PRECAUTIONS

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce dose or avoid coadministration. (2.2, 7.1, 12.3)
- Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use. (2.2, 7.2, 12.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Not recommended. (8.1)
- *Nursing Mothers:* Discontinue drug or discontinue nursing. (8.3)
- *Severe Hepatic Impairment:* Not recommended. (12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.5), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions (5.3)]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

ELIQUIS is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

ELIQUIS is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of ELIQUIS is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE *[see Clinical Studies (14.3)]*.

2.2 Dosage Adjustments

In patients with nonvalvular atrial fibrillation: The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Coadministration with strong dual CYP3A4 and P-gp inhibitors: For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) *[see Clinical Pharmacology (12.3)]*.

In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp *[see Drug Interactions (7.1)]*.

2.3 Missed Dose

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

2.4 Temporary Interruption for Surgery and Other Interventions

ELIQUIS 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. ELIQUIS 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 ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

2.5 Converting from or to ELIQUIS

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 initial INR measurements during the transition to 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.

Switching between ELIQUIS and anticoagulants other than warfarin: Discontinue one being taken and begin the other at the next scheduled dose.

2.6 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment.

Because patients with moderate hepatic impairment may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2)]*.

ELIQUIS is not recommended in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.7 Renal Impairment

The dosing adjustment for patients with moderate renal impairment and nonvalvular atrial fibrillation is described above *[see Dosage and Administration (2.2)]*. The recommended dose for nonvalvular atrial fibrillation patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age ≥80 years or body weight ≤60 kg) is present *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

No dose adjustment is required for the following indications:

- for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery.
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE.

2.8 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in 60 mL D5W and immediately delivered through a nasogastric tube (NGT) *[see Clinical Pharmacology (12.3)]*. Information regarding the administration of crushed and suspended ELIQUIS tablets swallowed by mouth is not available.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg, yellow, round, biconvex, film-coated tablets with "893" debossed on one side and "2½" on the other side.
- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with "894" debossed on one side and "5" on the other side.

ELIQUIS® (apixaban)

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.5) and Clinical Studies (14.1)]*.

5.2 Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

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) *[see Drug Interactions (7.3)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage (10)]*.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.4 Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

5.5 Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions (5.1)]*
- Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions (5.3)]*

ELIQUIS® (apixaban)

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14)]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI*)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.

† International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

‡ GI bleed includes upper GI, lower GI, and rectal bleeding.

§ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).

¶ Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.

** CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS dose, type of atrial fibrillation (AF), and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

ELIQUIS® (apixaban)

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

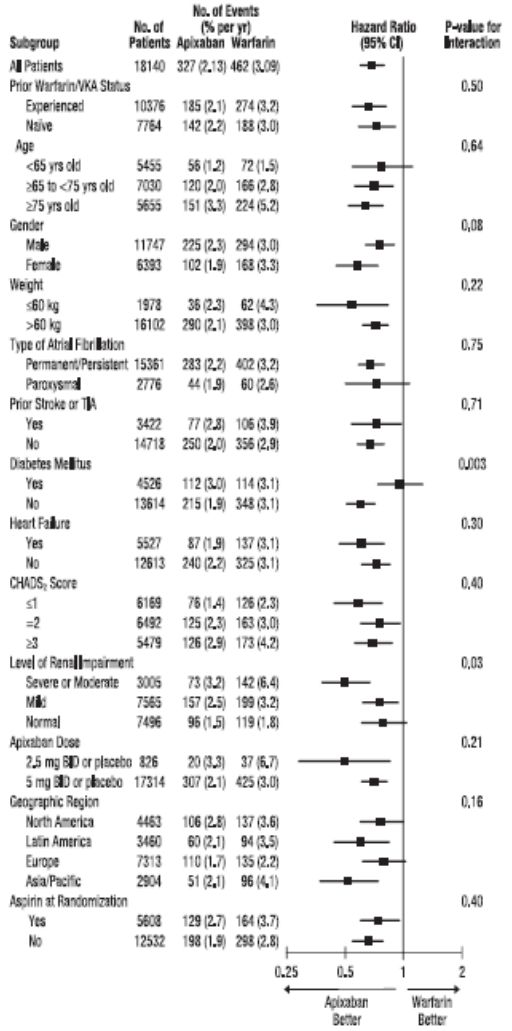


Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

ELIQUIS® (apixaban)

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery *(Continued)*

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg N=840 n (%)	ELIQUIS 5 mg N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg N=840 n (%)	ELIQUIS 5 mg N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

7 DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

7.1 Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

7.2 Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

7.3 Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77% per year with apixaban versus 0.62% per year with placebo in patients receiving single antiplatelet therapy and was 5.91% per year with apixaban versus 2.50% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

8.2 Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions (5.2)]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 End-Stage Renal Disease Patients Maintained with Hemodialysis

Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation for patients

with nonvalvular atrial fibrillation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥80 years or body weight ≤60 kg, reduce dose to 2.5 mg twice daily *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.2, 12.3)]*.

10 OVERDOSAGE

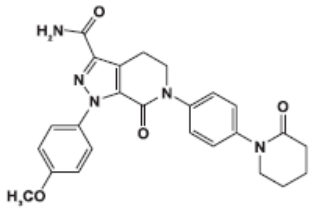
There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions (5.2)]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

11 DESCRIPTION

ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

ELIQUIS tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

12.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of apixaban.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel *[see Warnings and Precautions (5.2)]*. A 50% to 60% increase in anti-FXa activity was observed when apixaban was coadministered with enoxaparin or naproxen.

Specific Populations

Renal impairment: Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology

Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

12.3 Pharmacokinetics

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following administration of a crushed 5 mg ELIQUIS tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube (NGT), exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

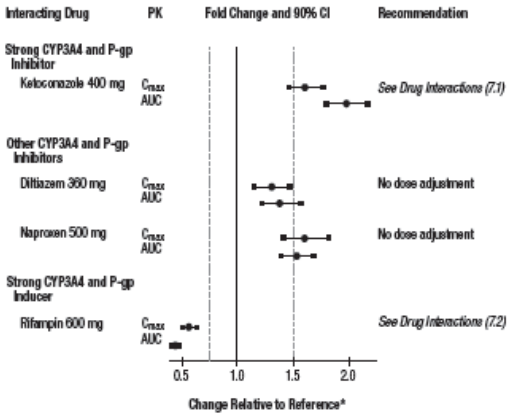
Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Drug Interaction Studies

In vitro apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

The effects of coadministered drugs on the pharmacokinetics of apixaban and associated dose recommendations are summarized in Figure 2 *[see also Warnings and Precautions (5.2) and Drug Interactions (7)]*.

Figure 2: Effect of Coadministered Drugs on the Pharmacokinetics of Apixaban



* Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations. Dosing recommendations were also informed by clinical considerations *[see Warnings and Precautions (5.2) and Drug Interactions (7)]*.

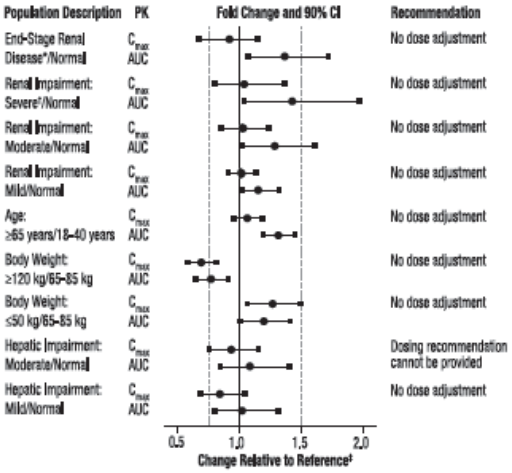
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of apixaban are summarized in Figure 3.

Figure 3: Effect of Specific Populations on the Pharmacokinetics of Apixaban



* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.

† Creatinine clearance 15 to 29 mL/min.

‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.

A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

In subjects with ESRD, a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours after administration of a single 5 mg dose of apixaban, the AUC of apixaban was 17% greater compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.

Protein binding was similar (92%-94%) between healthy controls and the on-dialysis and off-dialysis periods.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Mutagenesis: Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Impairment of Fertility: Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring

(F_1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F_1-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ARISTOTLE

Evidence for the efficacy and safety of ELIQUIS was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular AF comparing the effects of ELIQUIS and warfarin on the risk of stroke and non-central nervous system (CNS) systemic embolism. In ARISTOTLE, patients were randomized to ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) or to warfarin (targeted to an INR range of 2.0–3.0). Patients had to have one or more of the following additional risk factors for stroke:

- prior stroke or transient ischemic attack (TIA)
- prior systemic embolism
- age ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) "naive," defined as having received ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.

ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

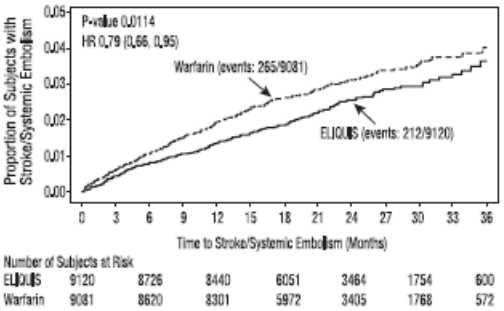
ELIQUIS also showed significantly fewer major bleeds than warfarin *[see Adverse Reactions (6.1)]*.

Table 9: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	Warfarin N=9081 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	
Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)	
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)	

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)



Number of Subjects at Risk

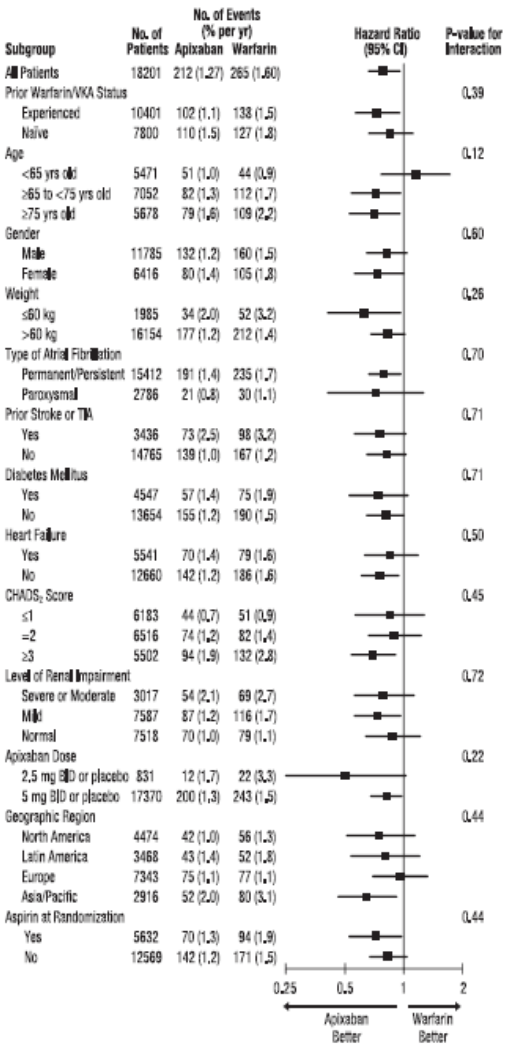
ELIQUIS	9120	8726	8440	6051	3464	1754	600
Warfarin	9081	8620	8301	5972	3405	1768	572

All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. ELIQUIS treatment resulted in a significantly lower rate of all-cause death ($p = 0.046$) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, $CHADS_2$ score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, ELIQUIS dose, type of AF, and aspirin use at randomization (Figure 5).

ELIQUIS® (apixaban)

Figure 5: Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



At the end of the ARISTOTLE study, warfarin patients who completed the study were generally maintained on a VKA with no interruption of anticoagulation. ELIQUIS patients who completed the study were generally switched to a VKA with a 2-day period of coadministration of ELIQUIS and VKA, so that some patients may not have been adequately anticoagulated after stopping ELIQUIS until attaining a stable and therapeutic INR. During the 30 days following the end of the study, there were 21 stroke or systemic embolism events in the 6791 patients (0.3%) in the ELIQUIS arm compared to 5 in the 6569 patients (0.1%) in the warfarin arm *[see Dosage and Administration (2.5)]*.

ELIQUIS® (apixaban)

AVERROES

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if ELIQUIS was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for ELIQUIS compared to aspirin that was associated with a modest increase in major bleeding (Table 10) *[see Adverse Reactions (6.1)]*.

Table 10: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	-
Hemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	-
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	-
MI	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	-
All-cause death	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	-

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of ELIQUIS is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥33 kg/m², and 625 patients with severe or moderate renal impairment.

In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either ELIQUIS 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period. In ADVANCE-3 and ADVANCE-2, the primary endpoint was tested for noninferiority, then superiority, of ELIQUIS to enoxaparin. In ADVANCE-1, the primary endpoint was tested for noninferiority of ELIQUIS to enoxaparin.

The efficacy data are provided in Tables 11 and 12.

Table 11: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
† Total VTE includes symptomatic and asymptomatic DVT and PE.
‡ Includes symptomatic and asymptomatic DVT.

Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			ADVANCE-2		
Events during 12-day treatment period	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE†/ All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT‡	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT‡	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
† Total VTE includes symptomatic and asymptomatic DVT and PE.
‡ Includes symptomatic and asymptomatic DVT.

The efficacy profile of ELIQUIS was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).

14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

Efficacy and safety of ELIQUIS for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following 6 to 12 months of anticoagulant treatment was derived from the AMPLIFY and AMPLIFY-EXT studies. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. All key safety and efficacy endpoints were adjudicated in a blinded manner by an independent committee.

AMPLIFY

The primary objective of AMPLIFY was to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with ELIQUIS 10 mg twice daily orally for 7 days followed by ELIQUIS 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, an existing heart valve or atrial fibrillation, or active bleeding were excluded from the AMPLIFY study. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

A total of 5244 patients were evaluable for efficacy and were followed for a mean of 154 days in the ELIQUIS group and 152 days in the enoxaparin/warfarin group. The mean age was 57 years. The AMPLIFY study population was 59% male, 83% Caucasian, 8% Asian, and 4% Black. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9%.

Approximately 90% of patients enrolled in AMPLIFY had an unprovoked DVT or PE at baseline. The remaining 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor in order to be randomized, which included previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

ELIQUIS was shown to be noninferior to enoxaparin/warfarin in the AMPLIFY study for the primary endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy (Table 13).

Table 13: Efficacy Results in the AMPLIFY Study

	ELIQUIS N=2609 n	Enoxaparin/Warfarin N=2635 n	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).
† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was consistent between the two subgroups.

AMPLIFY-EXT

Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulant therapy without having a recurrent event were randomized to treatment with ELIQUIS 2.5 mg orally twice daily, ELIQUIS 5 mg orally twice daily, or placebo for 12 months. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

A total of 2482 patients were randomized to study treatment and were followed for a mean of approximately 330 days in the ELIQUIS group and 312 days in the placebo group. The mean age in the AMPLIFY-EXT study was 57 years. The study population was 57% male, 85% Caucasian, 5% Asian, and 3% Black.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study. In the AMPLIFY-EXT study, both doses of ELIQUIS were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE), or all-cause death (Table 14).

Table 14: Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	ELIQUIS 2.5 mg N=840	ELIQUIS 5 mg N=813	Placebo N=829	ELIQUIS 2.5 mg vs Placebo	ELIQUIS 5 mg vs Placebo
	n (%)				
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

* Patients with more than one event are counted in multiple rows.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ELIQUIS (apixaban) tablets are available as listed in the table below.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
2.5 mg	Yellow, round, biconvex	Debossed with "893" on one side and "2½" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0893-21 0003-0893-41 0003-0893-31
5 mg	Pink, oval, biconvex	Debossed with "894" on one side and "5" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0894-21 0003-0894-41 0003-0894-31

Storage and Handling

Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions (5.3)]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations (8.1, 8.3)]*.
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

and

Pfizer Inc
New York, New York 10017 USA

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1289808A1 / 1289807A1 / 1298500A1

MEDICATION GUIDE

ELIQUIS® (ELL eh kwiss)
(apixaban)
tablets

What is the most important information I should know about ELIQUIS?

- **For people taking ELIQUIS for atrial fibrillation:**

  People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. ELIQUIS lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking ELIQUIS, you may have increased risk of forming a clot in your blood.

  Do not stop taking ELIQUIS without talking to the doctor who prescribes it for you. Stopping ELIQUIS increases your risk of having a stroke.

  ELIQUIS may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed ELIQUIS for you when you should stop taking it. Your doctor will tell you when you may start taking ELIQUIS again after your surgery or procedure. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- **ELIQUIS can cause bleeding** which can be serious and rarely may lead to death. This is because ELIQUIS is a blood thinner medicine that reduces blood clotting.

  You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, including:

  - aspirin or aspirin-containing products
  - long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (COUMADIN®, JANTOVEN®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to help prevent or treat blood clots

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist

if you are not sure if your medicine is one listed above.

While taking ELIQUIS:

- you may bruise more easily
- it may take longer than usual for any bleeding to stop

Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking ELIQUIS:

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

- **ELIQUIS is not for patients with artificial heart valves.**
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine
  - you take NSAIDs or a medicine to prevent blood from clotting
  - you have a history of difficult or repeated epidural or spinal punctures
  - you have a history of problems with your spine or have had surgery on your spine

  If you take ELIQUIS and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

ELIQUIS® (apixaban)

What is ELIQUIS?

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

It is not known if ELIQUIS is safe and effective in children.

Who should not take ELIQUIS?

Do not take ELIQUIS if you:

- currently have certain types of abnormal bleeding.
- have had a serious allergic reaction to ELIQUIS. Ask your doctor if you are not sure.

What should I tell my doctor before taking ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant. It is not known if ELIQUIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have **any** surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS. See "**What is the most important information I should know about ELIQUIS?**"

ELIQUIS® (apixaban)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ELIQUIS?

- **Take ELIQUIS exactly as prescribed by your doctor.**
- Take ELIQUIS twice every day with or without food.
- Do not change your dose or stop taking ELIQUIS unless your doctor tells you to.
- If you miss a dose of ELIQUIS, take it as soon as you remember. Do not take more than one dose of ELIQUIS at the same time to make up for a missed dose.
- Your doctor will decide how long you should take ELIQUIS. **Do not stop taking it without first talking with your doctor. If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke.**
- **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses.
- If you take too much ELIQUIS, call your doctor or go to the nearest hospital emergency room right away.
- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

What are the possible side effects of ELIQUIS?

- See **"What is the most important information I should know about ELIQUIS?"**
- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ELIQUIS. For more information, ask your doctor or pharmacist.

ELIQUIS® (apixaban)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ELIQUIS?

Store ELIQUIS at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ELIQUIS and all medicines out of the reach of children.

General Information about ELIQUIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELIQUIS for a condition for which it was not prescribed. Do not give ELIQUIS to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ELIQUIS that is written for health professionals.

For more information, call 1-855-354-7847 (1-855-ELIQUIS) or go to www.ELIQUIS.com.

What are the ingredients in ELIQUIS?

Active ingredient: apixaban.

Inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA
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Appendix 2 Bleeding Academic Research Consortium (BARC) Definition for Bleeding

- **Type 0**: no bleeding
- **Type 1**: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
- **Type 2**: any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
- **Type 3**
  - **Type 3a**
    - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - **Type 3b**
    - Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive agents
  - **Type 3c**
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
    - Subcategories confirmed by autopsy or imaging or lumbar puncture
    - Intraocular bleed compromising vision
- **Type 4**: CABG-related bleeding
  - Perioperative intracranial bleeding within 48 h
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding
  - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
  - Chest tube output ≥2L within a 24-h period
- **Type 5**: fatal bleeding
  - Type 5a
    - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
  - Type 5b
    - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
* Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin).
† Cell saver products are not counted.

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