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Clinical Trial Protocol: CV 185-373

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

Statistical Analysis Plan

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Author: Wen Hsieh
Senior Statistician, Biostatistics
Harvard Clinical Research Institute
930 Commonwealth Avenue
Boston, Massachusetts 02215

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Harvard Clinical Research Institute (HCRI) Signatures *Approvals below indicate that the individual has reviewed and agrees with this document as written. Any/All deviations will require amendments to this document.*			
Name	**Signature**	**Title/Department**	**Date**
Matthew Reynolds, MD, MSc,		Director, Economics and Quality of Life Research Harvard Clinical Research Institute Director of Electrophysiology Research, Division of Cardiology Lahey Hospital & Medical Center	
Christopher P. Cannon, MD		Executive Director, Cardiometabolic Trials Harvard Clinical Research Institute Cardiovascular Division Brigham and Women's Hospital Professor of Medicine, Harvard Medical School	

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Contents

1. 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

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

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]

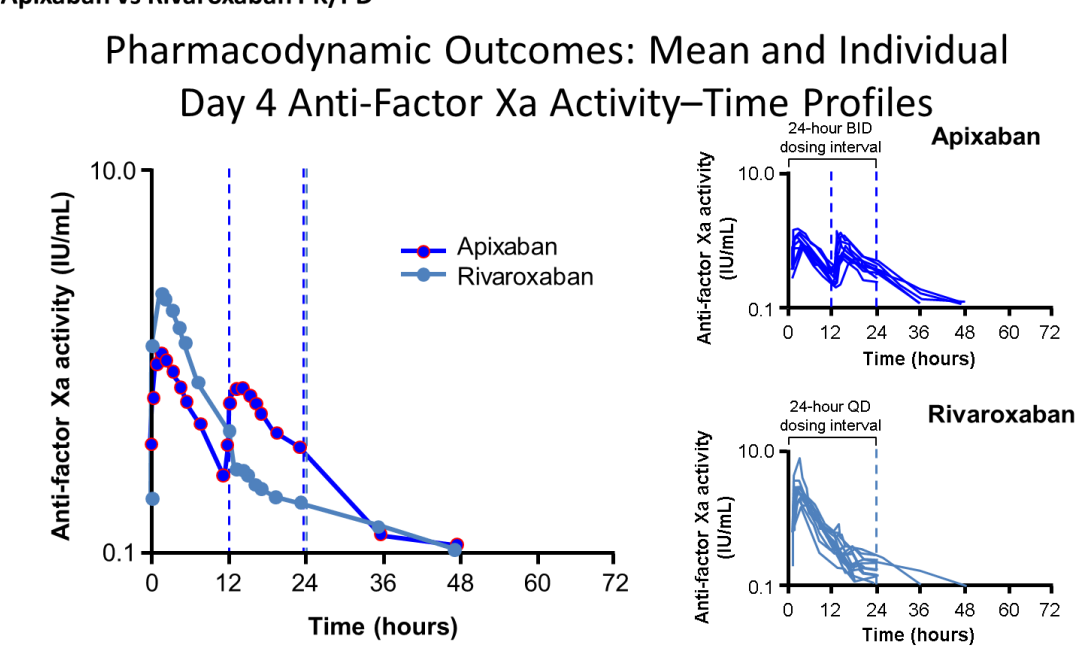
Considerable uncertainty exists about the optimal strategy for dosing NOAC agents around the time of an ablation procedure. "Uninterrupted" warfarin has become the standard approach based on case series and on randomized study (BRUISE CONTROL) of a related procedure[28-31]

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 bleeding and thrombotic 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. 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.

3. 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).

4. PRIMARY AND SECONDARY EDNPOINTS

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.

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

4.2 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.

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.

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.

5. INVESTIGATIONAL PLAN, STUDY DESIGN AND DURATION

This is a 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.

5.1 Prospective, Randomized Cohort

Subjects undergoing ablation for NVAF will be screened for eligibility and those meeting all eligibility requirements 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.

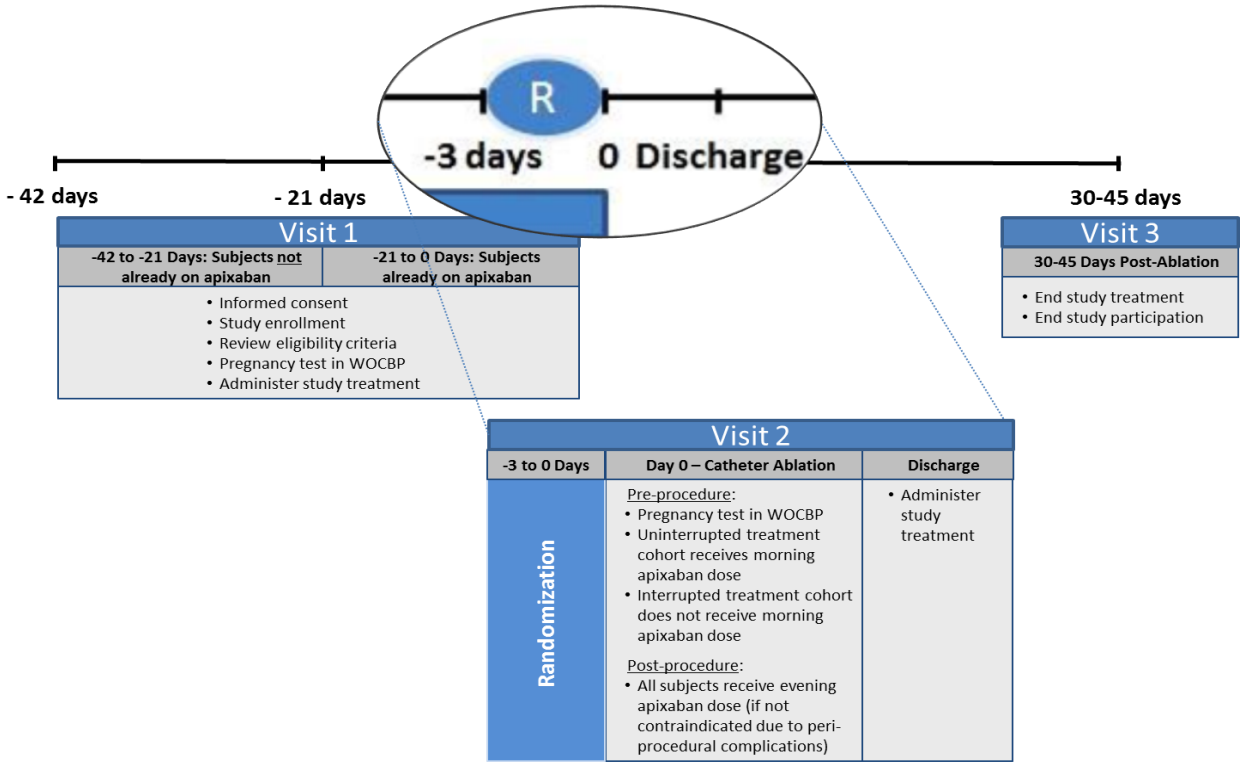
It is anticipated that up to 360 subjects may be enrolled in order to evaluate a total of 300 randomized subjects. Up to 20 sites in the United States (US) will participate. Subjects will be randomized in a 1:1 ratio to 2 peri-procedural treatment strategies (150 subjects per cohort):

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 the figure and Schedule of Events is shown in the table below.



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 in study protocol.
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 in study protocol.
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.

5.2 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.

6. STATISTICAL METHODOLOGY AND CONSIDERATIONS

6.1 Determination of Sample Size

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

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.

6.2 Analysis Populations

The following populations will be used for data analyses:

6.2.1 Intention-to-Treat (ITT)

All subjects randomized to either interrupted or uninterrupted apixaban.

6.2.2 Evaluable

The subset of the ITT population who underwent an index ablation procedure and were followed through 1 month (30 days minus an allowable 3-day visit window) post–index procedure or who experienced a primary endpoint prior to the 1 month follow-up visit. 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.

6.2.3 Safety

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

6.2.4 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. The time frame for analysis of events will be from the morning of the procedure through 30 days of follow-up.

6.3 Data Summaries

All statistical analyses will be performed after the study has completed and the database has been locked. All tables, statistical analyses, figures, and subject data listings will be generated using SAS® Version 9.4 or SAS EG Version 6.1 (SAS Institute Inc., Cary, North Carolina, United States of America). A subject who withdraws prior to the last planned observation will be included in the analyses up to the time of withdrawal.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum values). Unless otherwise specified, the mean and median for a continuous variable will be presented to 1 more decimal place than the original (raw) values and the SD will be presented to 2 more decimal places than the original values. The minimum and maximum will be presented to the same number of decimal places as the original values.

Categorical variables will be reported as frequency counts (including number missing) and the percentage of subjects in corresponding categories. Unless otherwise stated, percentage calculations will be based on the number of subjects with non-missing data in each of the treatment groups. Percentages will be presented to 1 decimal place. A percentage will not be presented against zero counts in the tables.

Individual subject data will be presented by subject in data listings. Data listings will include all data collected from the initial screening visit to the end of study for all subjects enrolled.

Given the pilot nature of this study, there is no significance level adjustment for multiple comparisons.

6.4 Subject Disposition

A tabulation of the number and percent of subjects will be presented for the following categories for each randomized treatment group:

- Screened
- Screen Failure (Percentages are based on number of Screened subjects)
- Randomization (Percentages are based on number of Screened subjects)
- Evaluable (Percentages are based on number of Randomized subjects)
- Number discontinued overall and by Reason for discontinuation (Percentages are based on number of Randomized subjects)
- Number of randomized patients in each study center (Percentages are based on total number of Randomized subjects)

6.5 Demography, Baseline Characteristics and Medical History

Descriptive statistics of demographic, baseline characteristics (age, gender, race, ethnicity, height, weight) and medical history 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.

6.6 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.

6.6.1 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.

To assess consistency of results across study sites, logistic regression on the primary endpoint with the independent variables of treatment, site and treatment-by-site interaction will be carried out on the evaluable analysis set. Significance of the treatment-by-site interaction will be assessed at the 0.15 level of significance. A non-significant interaction or a significant interaction that is only quantitative in nature will support the pooling of patients across study sites for the primary efficacy analysis. Sites with less than 10 patients will be pooled with other sites by geographic region; this will be done before the blind is broken.

6.6.2 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.

6.6.3 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).

6.7 Safety Analyses

Analyses on the primary safety endpoint (the incidence of clinically significant bleeding assessed from the time of randomization through 1 month post–catheter ablation) will be carried out in a similar manner as for the primary efficacy endpoint, including the assessment of the treatment-by-center interaction.

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.

6.8 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:

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

   $H1: \pi < 0.087$ (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 (<65 and ≥65 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) 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

6.9 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.

6.10 Protocol Deviation

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. 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.

A summary of major and minor protocol deviations for all ITT and evaluable populations will be presented for each apixaban group. Subjects will be counted once within each deviation category.

6.11 Concomitant Medication

Concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary. Incidence (number and percent of subjects reporting the medication at least once during the study) will be summarized for all concomitant medications. All verbatim descriptions and coded terms will be listed for all non-study medications.

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