PROACT Xa - A Trial to Determine if Participants With an On-X Aortic Valve Can be Maintained Safely on Apixaban (NCT04142658)

Protocol Version 1.0; 15 Jan 2020

Statistical Analysis Plan, V1.0; January 15, 2020

Statistical Analysis Plan, v1.4; January 11, 2023

This supplement contains the following items:

1. Protocol (first and final version).
2. Original and final versions of the statistical analysis plan with a summary of changes.

Title Page

Protocol Title: A prospective, randomized, active (warfarin) controlled, parallel-arm clinical trial to determine if patients with an On-X aortic valve can be maintained safely and effectively on the factor Xa inhibitor apixaban

Protocol Number: ONX1801.000-C (10/18)

Short Title: PROACT Xa

Study Locations: United States, Canada, Europe, Japan

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Regulatory Agency Identifier Number(s)

IND: 140178

EudraCT:

NCT: 04142658

WHO:

Other:

Approval Date: 16 January 2020

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16 Jan 2020

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1 Protocol Summary

Protocol Title: A prospective, randomized, active (warfarin) controlled, parallel-arm clinical trial to determine if patients with an On-X aortic valve can be maintained safely and effectively on the factor Xa inhibitor apixaban

Short Title: PROACT Xa

Rationale:

There is an unmet clinical need for an alternative to warfarin, such as a direct oral anticoagulant (DOAC), as anticoagulation in patients with an aortic mechanical prosthetic valve. Some patients may be genetically hyper- or hypo-responsive to warfarin, which makes management difficult. Another small group of patients is allergic to warfarin. A much larger group of patients has difficulty maintaining warfarin control due to dietary and drug interactions. Finally, the requirement for routine blood testing makes people reluctant to take warfarin. All of these factors drive younger patients in need of aortic valve replacement (AVR) toward selection of a tissue valve instead of a mechanical valve. Despite multiple studies (randomized, matched and risk adjusted) that show that tissue valves are associated with worse outcomes, younger patients choose this type of valve to avoid warfarin (Goldstone et al., 2017; Head et al., 2017; Glaser et al., 2016). In addition, multiple clinical studies have shown valve reoperation rates are higher for tissue valves used in these younger patients (McClure et al., 2010 and Bourguignon et al., 2016). Providing an alternative to warfarin anticoagulation may lead younger patients to choose a mechanical valve with greater durability and better clinical outcomes.

Objectives and Outcomes:

Co-Primary Efficacy Objectives
• To determine if apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism
• To determine if apixaban provides acceptable anticoagulation for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism compared with an objective performance criterion (OPC)[1]
Primary Safety Objective
• To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the safety outcome of major bleeding in patients with an On-X mechanical heart valve implanted in the aortic position
Secondary Efficacy Objectives

[1] On-X mechanical heart valve implanted in the aortic position refers to either an On-X Aortic Prosthetic Heart Valve or an On-X Ascending Aortic Prosthesis

• To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in patients with an On-X mechanical heart valve implanted in the aortic position
• To compare apixaban with warfarin (INR target range 2.0 – 3.0) for the individual components of the primary outcome (valve thrombosis and valve-related thromboembolism) in patients with an On-X mechanical heart valve implanted in the aortic position
• To compare apixaban with warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in pre-specified subgroups of patients with an On-X mechanical heart valve implanted in the aortic position

Overall Design:

This is a prospective, multicenter, open-label, randomized active controlled clinical trial to determine if apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in patients with an On-X mechanical heart valve implanted in the aortic position. A co-primary efficacy objective will determine if apixaban provides acceptable anticoagulation for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism compared with an OPC (Wu et al., 2014). Each participant will be followed for at least 2 years and each randomized arm will achieve at least 800 patient-years.

The study will consist of approximately 1000 participants (randomized 1:1 with approximately 500 participants in each of the apixaban and warfarin arms) at a minimum of 3 sites and up to 60 sites in North America, and potentially in Europe and/or Japan, who are 18 years of age or older, at least 3 months out from an On-X aortic valve implantation, and currently anticoagulated with warfarin.

Participants will be randomized to either continue warfarin with a target INR of 2.0 to 3.0 or switch to apixaban 5 mg twice daily (BID), or 2.5 mg BID in participants with 2 or 3 of the following characteristics:

- age ≥ 80 years
- weight ≤ 60 kilograms
- creatinine ≥ 1.5 mg/dL (133 micromol/L)

For participants randomized to apixaban, INR testing will be performed on the current warfarin dose with the following algorithm to initiate apixaban:

1. INR < 2; stop warfarin and start apixaban
2. INR 2.0 to 3.0; hold warfarin for 2 days, start apixaban on day 3
3. INR > 3.0 to 4.0; hold warfarin for 4 days, start apixaban on day 5
4. INR > 4.0; hold warfarin for 2 days, recheck INR, refer to steps 1, 2, or 3

Number of Participants:

Approximately 1000 participants will be randomly assigned to study intervention with an estimated total of 500 participants in the apixaban arm and 500 participants in the warfarin arm (see Section 8.2).

Intervention Groups and Duration:

All participants are expected to participate in this study for at least 2 years which includes the following study periods: screening/randomization, intervention, and follow-up. Participants will either continue warfarin with a target INR between 2.0 and 3.0, or switch to apixaban after randomization. A participant randomized to apixaban will start on apixaban 5 mg twice daily. If 2 of the following 3 characteristics are met at any time during the study, participants randomized to apixaban will be started on a reduced dose of 2.5 mg twice daily:

- age ≥ 80 years
- weight ≤ 60 kilograms
- creatinine ≥ 1.5 mg/dL (133 micromol/L)

Data Safety and Monitoring Board:

An independent Data Safety Monitoring Board (DSMB) will be responsible for the ongoing, independent evaluation of participants' safety. Clinical events, as outlined in Section 7, will be collected and reported overall and unblinded to study group to the DSMB. DSMB membership will be independent from the study investigators, and will consist of at least 3 members with at least 1 statistician and 1 cardiothoracic surgeon. The DSMB will review clinical outcomes and other safety concerns, and may recommend modification or termination of the trial if safety concerns warrant such a recommendation. The DSMB will establish criteria for recommending study termination, to the extent possible that the DSMB can predict adverse outcomes, before the proposed study begins. The DSMB will meet at least two times during the study in order to assure close and timely monitoring of clinical outcomes and safety. DSMB recommendations will be considered and acted upon by the academic leadership of the trial (Steering Committee) and the trial sponsor (CryoLife).

1.1 Schedule of Activities (SoA)

Procedure	Screening (up to 30 days before Day 1)[1]	Day 1 Randomization[2]	Every month (±14 days)	Intervention Period (Months)[1]								Final Study Visit	Notes
				1	2	3	6	12	18	24[3]	Every 6 months (±45 days) if applicable		
				(±14 days)			(±45 days)						
Informed consent	X												
Inclusion and exclusion criteria	X												
Pregnancy test	X												Serum or urine pregnancy test, women of childbearing potential
Demographics		X											
Medical history		X											
Prior warfarin history	X												
Concomitant medication review		X		X	X	X	X	X	X	X	X	X	
Valve characteristics		X											Including date and size of valve implant, conduit, etc.
Vital Signs		X						X		X	X[4]		Including pulse rate, blood pressure, and weight within 45 days before visit
Hemoglobin		X						X		X	X[4]		Obtained by study physician if no clinical results available within 45 days before visit
Serum creatinine		X						X		X	X[4]		
Randomization		X											Randomization initiates first 30-day supply of study drug

Procedure	Screening (up to 30 days before Day 1)[1]	Day 1 Randomization[2]	Every month (±14 days)	Intervention Period (Months)[1]								Final Study Visit	Notes
				1	2	3	6	12	18	24[3]	Every 6 months (±45 days) if applicable		
				(±14 days)			(±45 days)						
Call for supply of study medication			X										After the first study drug fill, a telephone call will occur to assess gaps and dosing changes prior to filling the next supply of study medication
INR levels		X	X										At least monthly INR testing required for participants randomized to warfarin. Assess for gaps in INR testing. INR obtained by study physician if no INR test results available within 37 days
Assess for thrombosis and thromboembolic events			X	X	X	X	X	X	X	X	X	X	
Assess for bleeding events			X	X	X	X	X	X	X	X	X	X	
Assess for changes in antithrombotic therapy (aspirin, anticoagulant)			X	X	X	X	X	X	X	X	X	X	
Assess quality of life and satisfaction with anticoagulation		X		X			X	X		X	X		EQ5D and Duke Anticoagulation Satisfaction Scale
Discontinue study drug and return to warfarin												X	

1. Month = 30 days.
2. Screening and Day 1 activities may be performed at the same visit.
3. Month 24 assessments will be performed if a participant withdraws early from the study (not just stops study drug but withdraws consent to participate). These assessments should be performed within 3 months after withdrawal.
4. Vital Signs, Hemoglobin, and Serum creatinine to be performed annually (at 12, 24, 36, and 48 months)

2 Introduction

PROACT Xa is designed to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained safely and effectively on the factor Xa inhibitor apixaban (Eliquis). The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated participants to updated OPC for FDA-approved mechanical heart valves in the aortic position. This is an open-label study in which patients who are at least 3 months out from implantation of an On-X valve in the aortic position will be randomized in a 1:1 fashion to either apixaban 5 mg twice daily or 2.5 mg twice daily in selected participants meeting reduced dose criteria or warfarin adjusted to an INR of 2.0-3.0. Participants will be followed for at least 2 years after randomization with at least 800 patient-years of follow-up in each randomized group. If the primary efficacy hypothesis is proven, the data will be used to support a change in the On-X valve device label to state that apixaban is an acceptable alternative to warfarin for anticoagulation in patients 3 or more months after implantation of an On-X valve in the aortic position.

2.1 Study Rationale

There is an unmet clinical need for an alternative to warfarin, such as a direct oral anticoagulant (DOAC), as anticoagulation in patients with an aortic mechanical prosthetic valve. Some patients may be genetically hyper- or hypo-responsive to warfarin, which makes management difficult. Another small group of patients is allergic to warfarin. A much larger group of patients has difficulty maintaining warfarin control due to dietary and drug interactions. Finally, the requirement for routine blood testing makes people reluctant to take warfarin. All of these factors drive younger patients in need of aortic valve replacement toward selection of a tissue valve instead of a mechanical valve. Despite multiple studies (randomized, matched and risk adjusted) that show that tissue valves are associated with worse outcomes, younger patients choose this type of valve to avoid warfarin (Goldstone et al., 2017; Head et al., 2017; Glaser et al., 2016). In addition, multiple clinical studies have shown valve reoperation rates are higher for tissue valves used in these younger patients (McClure et al., 2010 and Bourguignon et al., 2016). Providing an alternative to warfarin anticoagulation may lead younger patients to choose a mechanical valve with greater durability and better clinical outcomes.

2.2 Background

The On-X Prosthetic Heart Valve is a bileaflet mechanical heart valve, which consists of an orifice housing and 2 leaflets. The prosthesis was originally approved by the Food and Drug Administration in 2001 with more than 200,000 implants worldwide. There have been multiple studies and publications evaluating the valve's safety and efficacy in the aortic position (Palatianos et al., 2007, McNicholas et al., 2006, and Chambers et al., 2013). Multicenter premarket clinical studies conducted in Europe (Palatianos et al., 2007) and North America (McNicholas et al., 2006) exhibited low thromboembolic (TE) rates at 0.88 and 0.9 %/patient-year (pt-yr). Longer-term data of up to 12 years was reported on 214 patients (Chambers et al., 2013) for On-X valves in the aortic position demonstrating a low rate of adverse clinical events and TE rate of 0.6%/pt-yr. An interesting finding that stood out in these reported studies was the low rate of thrombosis with the On-X valve in the aortic valve position. The preclinical and

clinical history of the On-X valve includes studies looking at thrombotic potential and studies in poorly anticoagulated populations. Flameng et al., 2002 conducted a study of the valve in a non-anticoagulated sheep model designed to predict resistance to thrombosis and found that the On-X valve statistically outperformed both the St. Jude Medical (SJM) and Carbomedics (CMI) valves. The first thrombosis of an On-X valve occurred at 6 weeks compared to 2 weeks for the other 2 valves. Additionally, 2 of 6 test valves survived the test without thrombosis compared to 0 of 7 valves for the others. A South African clinical trial conducted by Wu et al., 2006 assessed 104 On-X valves in the aortic position with no or inadequate anticoagulation in up to 40% of the study population. Despite these limitations in anticoagulation management, there was no valve thrombosis and a TE rate of 1.1%/pt-yr. Given these favorable clinical outcomes, the On-X valve was believed to be an ideal candidate to assess using an alternate anticoagulation strategy. These data formed the basis for the Prospective Randomized On-X Valve Anticoagulation Clinical Trial (PROACT trial) investigating the safety and efficacy of lower anticoagulation goals with the On-X valve (ClinicalTrials.gov number, NCT00291525).

On-X Life Technologies conducted a study looking at the use of reduced anticoagulation therapy, (ie, warfarin with a lower target INR of 1.5 to 2.0) (Puskas et al., 2014 and Puskas et al., 2018) 3 months after valve implantation. The PROACT trial was conducted in 375 patients at high risk of thromboembolism (eg, atrial fibrillation, low ejection fraction, or enlarged left atrium). With a mean follow-up of 3.8 years, the mean INR was 2.50 ± 0.63 for the control and 1.89 ± 0.49 for the test groups ($P < .0001$). The participants anticoagulated with a lower target INR had significantly lower incidence of major (1.59% vs 3.94%/pt-yr; $P = 0.002$) and minor (1.27% vs 3.49%/pt-yr; $P = 0.002$) bleeding. The incidence of stroke, transient ischemic attack, total neurologic events, and all-cause mortality were not significantly different between the 2 groups.

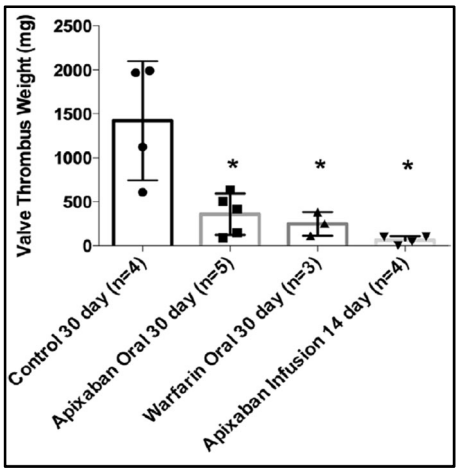
An alternative to warfarin is the use of one of the DOACs. These drugs fall generally into 2 categories: direct thrombin inhibitors and factor Xa inhibitors. DOACs, including the thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban), have been approved for use in patients with nonvalvular atrial fibrillation; apixaban and rivaroxaban have also been approved for the prevention and treatment of venous thromboembolism.

A trial of dabigatran in patients with mechanical valves (RE-ALIGN) was conducted and ultimately halted due to increases in both bleeding and thrombotic events with dabigatran compared to warfarin (Eikelboom et al., 2013). The reason for these poor results is ultimately unclear. Study design may be a contributor as the study examined multiple dabigatran doses, multiple drug ‘conversion’ strategies, valves in all positions and all brands of mechanical valves. Additionally, RE-ALIGN included patients with newly implanted valves, and clinical outcomes were worse in these patients. Our hypothesis is that the favorable mechanical features of the On--X valve, will permit a higher likelihood of success with use of a DOAC than observed in the RE-ALIGN study. This trial differs from the RE-ALIGN trial design by including a single implant position (aortic), a single valve type (On-X aortic valve or On-X AAP), and excluding patients who are within 3 months from valve implantation surgery.

In addition to modifications in trial design and valve type versus the RE-ALIGN trial, PROACT Xa will be conducted using the factor Xa inhibitor, apixaban. Apixaban has a favorable bleeding profile and similar thromboembolism prevention compared with warfarin (Granger et al., 2011). For mechanical valves, a preclinical study was performed using a heterotopic aortic valve porcine model with bileaflet mechanical aortic valve implants (Lester et al., 2017). In the 4 randomized

groups, postmortem valve thrombus weight was lowest in the apixaban infusion group, see Figure 1. The apixaban infusion group dose was modeled after human pharmacokinetic data based on the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation study (ARISTOTLE) (Granger et al., 2011). The apixaban infusion was designed to mimic the human 5 mg oral twice daily area under the curve values. These results suggest that apixaban may be a viable alternative to warfarin for thromboprophylaxis of the On-X valve.

Figure 1. Comparison of valve thrombus weight.



2.3 Benefit/Risk Assessment

2.3.1 Benefits

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

In the ARISTOTLE trial comparing apixaban to warfarin for the prevention of stroke and systemic embolism in NVAF patients, apixaban was found to be superior to warfarin for the prevention of stroke or systemic embolism (1.27% per year on apixaban versus 1.60% on warfarin, HR 0.79, 95% CI 0.66 to 0.95, $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority). In addition, apixaban was found to cause significantly less bleeding than warfarin (major bleed on apixaban 2.13% versus 3.09% on warfarin, HR 0.69, 95% CI 0.60 to 0.80, $p < 0.001$) and resulted in a significant reduction in all-cause mortality (3.52% on apixaban versus 3.94% on warfarin, HR 0.89, 95% CI 0.80 to 0.99, $p = 0.047$).

2.3.2 Risks

As with other anticoagulants, patients administered apixaban are to be carefully observed for signs of bleeding. Apixaban is recommended to be used with caution in patients with increased risk of hemorrhage, such as congenital or acquired bleeding disorders; active ulcerative GI disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of hemorrhagic

stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery. Apixaban is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Limited clinical data in patients with severe renal impairment indicate that apixaban plasma concentrations are increased in this patient population; therefore, apixaban should be used with caution in these patients because of a potentially higher bleeding risk. The trial will exclude patients who have severe renal impairment or who are on concomitant combined strong P-gp and CYP3A4 inducers or inhibitors given their drug-drug interactions with apixaban. Detailed information about the known and expected benefits and risks and reasonably expected adverse events of apixaban may be found in the Package Insert.

3 Objectives and Outcomes

Co-Primary Efficacy Objective
• To determine if apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism • To determine if apixaban provides acceptable anticoagulation for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism compared with an objective performance criterion
Primary Safety Objective
• To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the safety outcome of major bleeding in patients with an On-X mechanical heart valve implanted in the aortic position
Secondary Efficacy Objectives
• To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in patients with an On-X mechanical heart valve implanted in the aortic position
• To compare apixaban with warfarin (INR target range 2.0 – 3.0) for the individual components of the primary outcome (valve thrombosis and valve-related thromboembolism) in patients with an On-X mechanical heart valve implanted in the aortic position
• To compare apixaban with warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in pre-specified subgroups of patients with an On-X mechanical heart valve implanted in the aortic position

4 Study Design

4.1 Overall Design

This is a prospective, multicenter, open-label, randomized, active controlled clinical trial to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained safely and effectively on apixaban. The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated participants to updated OPC for FDA-approved mechanical heart valves in the aortic position. Each participant will be followed for at least 2 years and each randomized arm will achieve at least 800 patient years.

The study will consist of approximately 1000 participants (randomized 1:1 with approximately 500 participants in the apixaban arm and 500 participants in the warfarin arm) at a minimum of 3 sites and up to 60 sites in North America, and potentially in Europe and/or Japan, who are 18 years of age or older, at least 3 months out from an On-X aortic valve implantation, and currently managing their anticoagulation with warfarin.

Participants will be randomized to either continue warfarin or switch to apixaban. Participants randomized to apixaban will receive 5 mg twice daily (BID), or apixaban 2.5 mg BID in participants with 2 or 3 of the following characteristics:

- age ≥ 80 years
- weight ≤ 60 kilograms
- creatinine ≥ 1.5 mg/dL (133 micromol/L)

For participants randomized to apixaban, INR testing will be performed on the current warfarin dose with the following algorithm to initiate apixaban:

1. INR < 2; stop warfarin and start apixaban
2. INR 2.0 to 3.0; hold warfarin for 2 days, start apixaban on day 3
3. INR > 3.0 to 4.0; hold warfarin for 4 days, start apixaban on day 5
4. INR > 4.0; hold warfarin for 2 days, recheck INR, refer to steps 1, 2, or 3

4.2 Scientific Rationale for Study Design

Warfarin has long been the main-stay of thromboembolism prophylaxis for participants with mechanical heart valves. In patients with non-valvular atrial fibrillation, a number of non-warfarin anticoagulation (DOAC) alternatives have been developed and received FDA approval. Among these, apixaban is one of two DOACs shown to be superior to warfarin in both efficacy and safety (Granger et al., 2011) and provides similar levels of *in vitro* anticoagulation. Additionally, the On-X valve implanted in the aortic position has been shown to be safe with lower levels of anticoagulation – outcomes of a target INR 1.5-2.0 non-inferior to those of a target INR 2.0-3.0 (Puskas et al., 2018). Note, while composite mechanical valves assembled during surgery were included in the PROACT trial, the On-X AAP device was not commercially available at the time of the trial and has, thus, not been assessed with low INR. For these

reasons, the PROACT-Xa trial has selected apixaban to study as an alternative to warfarin in participants with On-X mechanical valves implanted in the aortic position, hypothesizing that apixaban will be non-inferior to warfarin in preventing mechanical valve-related thromboembolism. The primary events of interest include thrombosis of the mechanical valve itself, as well as thromboembolic events, such as stroke, transient ischemic attacks, or myocardial infarction, related to thrombus formed on the valvular apparatus. For patients who require aortic valve replacement, clinicians engage in shared decision-making that prioritizes selection of a valve that is durable and safe. Mechanical heart valves are a much more durable option than bioprosthetic valves, and are preferred for patients of younger ages to reduce the need for reoperation. However, safe warfarin anticoagulation requires frequent INR testing and dietary restrictions to reduce INR lability that may be cumbersome. The ability to safely anticoagulate a patient with a mechanical heart valve with a DOAC would directly benefit participants, not only in convenience of treatment and treatment monitoring, but also expanding the ability to receive a mechanical heart valve if these considerations were what led to selection of a bioprosthetic valve previously. The demonstrated relative bleeding advantage of apixaban over warfarin in the atrial fibrillation population would be expected to be maintained among patients with an On-X mechanical valve implanted in the aortic position. Should that prove to be the case, then apixaban may provide a safe, effective, and convenient alternative to warfarin for patients with On-X aortic valves.

4.3 Justification for Dose

This study will use a previously-established apixaban dose of 5 mg twice daily that was shown to be superior to warfarin in preventing stroke or other thromboembolic events in participants with atrial fibrillation. For participants who meet 2 or more of the following characteristics: age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL or more, a commercially available lower dose of apixaban (2.5 mg twice daily) will be used, consistent with prior trials. Patients receiving combined strong P-gp and CYP3A4 inhibitors/inducers will be excluded from the trial. For additional information regarding the apixaban 2.5 mg dose, refer to Section 5.7.

4.4 End of Study Definition

End of Study occurs when the last enrolled participant has completed the 2-year follow-up visit and at least 800 patient-years of cumulative follow-up has been reached in each randomized arm.

4.5 Study Population

Approximately 1000 patients who are at least 3 months out from an On-X mechanical valve implanted in the aortic position and receiving warfarin anticoagulation will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.5.1 Inclusion Criteria

Participants are eligible to be included in the study if all of the following criteria apply:

1. Male or female at least 18 years of age at the time of giving informed consent.
2. Able to receive warfarin with a target INR 2.0 to 3.0.
3. Able to take low-dose aspirin at a dose of 75 -100 mg daily or have a documented contraindication to aspirin use.
4. Implantation of an On-X mechanical valve in the aortic position at least 3 months (90 days) prior to enrollment

5. If female participant of childbearing potential, including those who are less than 2 years post-menopausal, she must agree to and be able to use a highly effective method of birth control (eg, barrier contraceptives [condom or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], intrauterine devices or sexual abstinence) continuously through the study until the last study visit.
6. Able to provide written informed consent.

4.5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Mechanical valve in any position other than aortic valve.
2. Any cardiac surgery in the 3 months (90 days) prior to enrollment
3. Need to be on aspirin >100 mg daily or a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel, or ticlopidine).
4. Known hypersensitivity or other contraindication to apixaban.
5. On dialysis or a creatinine clearance < 25 mL/min.
6. Experienced an ischemic stroke or intracranial hemorrhage within 3 months of screening for enrollment.
7. Active pathological bleeding at the time of screening for enrollment
8. Active endocarditis at the time of screening for enrollment.
9. Pregnant at the time of screening for enrollment, plan to become pregnant at any point during the study, or are breast feeding at the time of screening for enrollment.
10. On concomitant combined strong P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inducers or inhibitors
11. History of non-compliance with recommended monthly INR testing

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4.6 Lifestyle Considerations

Participants receiving warfarin during this study will need to eat a normal, balanced diet maintaining a consistent amount of vitamin K and should avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables.

4.7 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5 Study Intervention(s)/Test Article(s) Administered

5.1 Study Drugs

Table 1 Study Drugs

ARM Name	Apixaban	Warfarin
Intervention Name	apixaban	warfarin
Type	Factor Xa inhibitor (anticoagulant)	vitamin K antagonist (anticoagulant)
Dose Formulation	tablet	tablet
Dosage Level(s)	5 mg twice daily, or 2.5 mg twice daily if 2 or more of the following 3 criteria are met: - age ≥80 years - body weight ≤60 kg - serum creatinine ≥1.5 mg/dL	As directed by primary anticoagulation-managing clinician targeting INR levels of 2-3
Route of Administration	oral	oral
Sourcing	Study drug supplied by designated drug distribution center	Study drug supplied by designated drug distribution center
Packaging and Labeling	Study drug will be provided in a container that will be labeled as required per country requirement.	Study drug will be provided in a container that will be labeled as required per country requirement.

5.2 Medical Devices

Inclusion criteria for this study require that participants have an On-X aortic valve replacement, including the On-X Ascending Aortic Prosthesis, and are at least 3 months from implantation.

The On-X Prosthetic Heart Valve is a bileaflet mechanical heart valve, which consists of an orifice housing and 2 leaflets. The orifice inflow area has a flared inlet designed to reduce flow turbulence, and the outflow rim consists of leaflet guards designed to protect the leaflets while in the closed position. The leaflets rotate around tabs located in the inner circumference of the orifice ring. In the closed position, each leaflet forms a nominal angle of 40° relative to the plane of the orifice. In the open position, the plane of each leaflet forms a nominal angle of 90° relative to the plane of the orifice. The leaflets have a travel arc of 50° to the closed position. The orifice is composed of graphite substrate coated with On-X Carbon, a pure unalloyed form

of pyrolytic carbon. The leaflets consist of On-X Carbon deposited on a graphite substrate, which is impregnated with 10 weight% tungsten to provide radiopacity. The sewing ring is constructed of polytetrafluoroethylene (PTFE) fabric mounted on the orifice using titanium retaining rings and 5-0 suture material. This form of sewing ring attachment to the orifice allows for rotation of the sewing ring in situ during implantation. Orientation reference marks are provided on the sewing ring for valve orientation.

The On-X Prosthetic Heart Valve is available in 3 aortic sewing ring configurations. All aortic configurations are available in sizes 19, 21, 23, 25 and 27/29 mm. Aortic valves, size 19 mm through 25 mm, are designed for intrasupra-annular sewing ring position, while the valve size 27/29 mm is designed for intra-annular sewing ring position.

The On-X Prosthetic Heart Valve was originally approved by the Food and Drug Administration in 2001 with more than 260,000 implanted worldwide to date.

The On-X Ascending Aortic Prosthesis combines the On-X Prosthetic Heart Valve and the Gelweave Valsalva™ Vascular Prosthesis. The Gelweave Valsalva is incorporated into the cuff structure of the On-X valve to create the Ascending Aortic Prosthesis (AAP). The AAP is available in sizes 19, 21, 23, 25 and 27/29 mm. The On-X AAP has been commercialized since 2011 with more than 7,000 shipments. The On-X Ascending Aortic Prosthesis was approved by the Food and Drug Administration in 2011.

5.3 Preparation/Handling/Storage/Accountability

Both apixaban and warfarin are commercially available. After informed consent, participants will be randomized in a 1:1 ratio to receive apixaban or warfarin in an open-label fashion. Participants randomized to warfarin will undergo INR testing with warfarin dosing conducted based on recommended monthly INR levels, targeting an INR of 2.0-3.0. INR monitoring can be done by the site investigator or designee (including the participant's prior INR manager) or by home monitoring, with the site investigator providing oversight and guiding dose adjustments. Participants randomized to either apixaban or warfarin will obtain their study medication from a designated drug distribution center, with monthly telephone contact to coordinate medication resupply.

5.4 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized in a 1:1 ratio to receive apixaban or warfarin. An unmasked study statistician will generate the randomization schedule and this schedule and stratification scheme will be pre-programmed into the randomization module of the EDC database. All randomizations will be performed using the EDC-embedded randomization module.

This is an open- label study; potential bias will be reduced by having outcome events adjudicated by reviewers blinded to study drug assignment using standardized criteria. Randomization will be stratified by whether the On-X valve was implanted within or greater than 1 year of study enrollment; this stratification is designed to reduce potential bias introduced by inter-site differences in participant recruitment strategies.

5.5 Study Intervention Compliance

For participants randomized to apixaban, participant compliance with the study intervention will be assessed by filling of the drug with a gap in filled supply >14 days defined as non-

compliance. For participants randomized to warfarin, participant compliance with the study intervention will be assessed by INR levels. Site investigators will advise and reinforce with the participant the importance of regular INR monitoring. Participants will undergo at least monthly INR monitoring; monitoring can be done by the site investigator or designee (including the participant's prior INR manager) or by home monitoring. Study investigators will closely monitor all participants randomized to warfarin with collection of at least monthly INR data to maximize time in therapeutic range (INR levels between 2.0 and 3.0). If INR results measured by the designee or home monitoring repeatedly trend outside of acceptable therapeutic range, the site investigator will conduct INR testing as needed and/or guide warfarin dose adjustments to achieve target INR levels between 2.0 and 3.0. If a >37-day gap in INR measurement occurs, the site investigator will contact the participant to perform INR testing. All INR values will be recorded on the eCRF and the time in therapeutic range for the warfarin arm will be calculated and results will be provided to the DSMB. Satisfaction with anticoagulation will be assessed using the Duke Anticoagulation Satisfaction Scale (Samsa et al., 2004).

5.6 Concomitant Therapy

All concomitant medications will be self-reported by the participant or abstracted from the medical records. Participants will report concomitant medications throughout the study as specified in the Schedule of Activities.

Details on the use of aspirin and other antithrombotic medications will be collected at baseline and during study follow-up as specified in the Schedule of Activities. Participants should take low-dose aspirin at a dose of 75 - 100 mg daily as recommended by current practice guidelines, unless there is a documented contraindication to the use of aspirin.

5.7 Dose Modification

Participants randomized to apixaban will be dosed at 5 mg twice daily, unless they meet at least 2 of the following criteria for dose reduction to 2.5 mg twice daily as per the apixaban package label:

- Age ≥ 80 years
- Weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL (133 micromol/L)

Participants randomized to apixaban 5 mg twice daily will have their dose decreased if he/she meets at least 2 of the 3 criteria at any time during the study.

Participants randomized to warfarin should be titrated to an INR target goal of 2.0 to 3.0. Dosages of warfarin to achieve that range will be directed by the site investigator or designee (including the participant's prior INR manager) or by home monitoring. If a > 37-day gap in INR measurement occurs or if INR results measured by the designee or home monitoring repeatedly trend outside of acceptable therapeutic range, the site investigator will conduct INR testing as needed and/or guide warfarin dose adjustments to achieve target INR levels between 2.0 and 3.0. All INR values will be recorded on the eCRF.

5.8 Intervention after the End of the Study

After the completion of the last follow-up visit for the study, all participants randomized to apixaban will be returned to warfarin therapy at a dose judged appropriate by the treating physician; e.g. based on the clinical profile of the subject including age, dry body weight or

hemodialysis target body weight, creatinine clearance, concomitant therapies or other clinical conditions. A resource that can be used to choose initial dose is www.warfarindosing.org. On the day following the final study-mandated apixaban dose, warfarin will be initiated so that the participant will take both apixaban and warfarin until an INR of at least 2.0 has been obtained. As soon as the INR level is ≥2.0, apixaban will be discontinued.

5.9 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

For participants randomized to apixaban who develop a thrombotic or major bleeding event, the study investigator or designee will decide whether the participant should continue with apixaban, temporarily pause apixaban, or return to standard warfarin therapy. Such decisions are at the discretion of the participant's treating clinician. Participants who are returned to warfarin (section 5.8) or stop anticoagulation, regardless of whether or not they have either a thrombotic or major bleeding event, will continue to be followed in the study.

5.9.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study drug (apixaban or warfarin). If study drug is permanently discontinued, the participant will remain in the study for all follow-up visits. See the SoA for data to be collected at the time of discontinuation of study drug.

5.9.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

5.9.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site and no information can be obtained about the participant's primary outcome and vital status.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site staff must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before the participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address

or local equivalent methods). These contact attempts should be documented in the participant's medical record. Where possible, the participant's medical record should be searched for evidence of vital status and thromboembolic and bleeding clinical outcome events (eg, clinic, telemedicine, or hospitalization encounters).

6 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions will not be allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The protocol includes screening participants for symptoms suggestive of valve thrombosis, such as new onset heart failure (dyspnea, edema, etc) or thromboembolic phenomena (e.g., hospitalization for stroke or urgent revascularization). This will be implemented via a standardized questionnaire at monthly intervals. Additional imaging (echocardiography, CT, MRI, angiography, and/or non-cardiac ultrasound), selected based on clinical indication, will be pursued for participants that report symptoms or signs potentially suggestive of valve thrombosis or valve-related thromboembolism. Imaging results will be collected to independently adjudicate whether or not valve thrombosis or valve-related thromboembolism occurred.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.1 Efficacy Assessments

Efficacy will be assessed by the evaluation of the hazard rates of the primary efficacy outcome, the composite of valve thrombosis and valve-related thromboembolism. An independent Clinical Events Classification (CEC) Committee will adjudicate whether any valve thrombosis and/or valve-related thromboembolism event has occurred.

Valve thrombosis: defined as any thrombus not caused by infection attached to or near an implanted On-X valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment other than continued oral anticoagulation. Furthermore, valve thrombus found at autopsy in a participant whose cause of death was not valve related or found at operation for an unrelated indication will also be reported as valve thrombosis. (Akins et al., 2008).

Valve-related thromboembolism: defined as any thromboembolic stroke, thromboembolic transient ischemic attack (TIA), thromboembolic myocardial infarction, or arterial

thromboembolism to another organ or limb, occurring after the immediate perioperative period and not associated with infection or intracardiac tumor. The independent CEC committee will determine whether a thromboembolism was related to the On-X valve based on clinical evaluation, surgery, and autopsy data. If the thromboembolism is determined to be of unknown origin after clinical evaluation, surgery, and/or autopsy, the thromboembolism will be conservatively considered to be related to the On-X valve.

6.2 Safety Assessments

Safety will be assessed by the evaluation of the hazard rates of the primary safety outcome, major bleeding, defined as any episode of internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion, pericardiocentesis or reoperation. Bleeding will be adjudicated by the CEC Committee. Secondary definitions of bleeding, including Bleeding Academic Research Consortium (BARC) and International Society of Thrombosis and Hemostasis (ISTH) definitions of bleeding, will also be adjudicated.

Planned time points for all safety assessments are provided in the SoA.

6.3 Other Assessments

Vital Signs
At day 1 (randomization) and yearly thereafter, data on pulse rate, blood pressure, and weight will be collected. If no clinical results are available within 45 days before the visit, an in-person visit will be required to collect these data.

Clinical Safety Laboratory Assessments
At day 1 (randomization) and yearly thereafter, study investigators will obtain hemoglobin and serum creatinine levels. If no clinical results are available within 45 days before the visit, an in-person visit will be required to collect these data.

7 Adverse Events (AEs) and Serious Adverse Events (SAEs)

Because apixaban and warfarin have both been extensively studied and used clinically and have well established safety profiles in populations similar to and at higher-risk of adverse outcomes than those with an On-X mechanical aortic valve prosthesis, only the specific serious and non-serious AEs listed in this section will be collected and reported.

The following suspected events will be collected on the eCRF and adjudicated by the CEC:

- valve thrombosis or dysfunction (see Section 7.3)
- stroke or TIA
- myocardial infarction
- arterial thromboembolism
- bleeding
- hospitalization and the reason for hospitalization
- death and the cause of death

7.1 Time Period and Frequency for Collecting AE Information

All clinical events will be collected from the signing of the informed consent form (ICF) until the final visit at the time points specified in the SoA (Section 1.1).

Events that begin before randomization but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF.

7.2 Regulatory Reporting Requirements for SAEs

Clinical events, as outlined in Section 7, will be collected and reported in aggregate and unblinded to study group to the Data Safety Monitoring Board (DSMB). Other serious adverse events will not be collected. The study DSMB will be responsible for the ongoing evaluation of participants' safety (eg, event trends). Site investigators may report individual SAEs to their IRBs according to their local IRB requirements.

7.3 Medical Device Incidents (Including Malfunctions, ADEs, UADEs)

Inclusion criteria for this study require that participants have an On-X aortic valve replacement and are at least 3 months following implantation. In order to fulfill regulatory reporting obligations worldwide, investigators are responsible for the detection and documentation of events meeting the definitions of device incident or malfunction that occur during the study.

The definition of a Medical Device Incident can be found in Section 10.1.

All valve-related Adverse Device Effects (ADEs) and Unanticipated Adverse Device Effects (UADEs) occurring from informed consent through the final study visit will be collected. ADEs and UADEs will be reported in aggregate unblinded to study group to the DSMB.

Investigators are responsible for reporting UADEs to their IRB within 10 working days of first learning of the event as per local requirements.

It is understood that complete information about an event may not be known at the time the initial report is recorded. The investigator must assess the causal relationship of the event to the study drug and the investigational device (including rationale for assessment) and should make every attempt to obtain as much information as possible concerning the event. Additional

information pertaining to an event should be reported as it becomes available. All UADEs will be followed to resolution or stabilization. Stabilization means the investigator does not expect any further improvement or worsening of the AE.

7.4 Treatment of Overdose

For this study, the following will be considered an overdose:

- any dose of apixaban greater than 15 mg within a 24-hour time period
- any dose of warfarin resulting in an INR above 7

No specific treatment is recommended for an overdose of apixaban or warfarin. If major bleeding occurs in the setting of an overdose of apixaban, prothrombin complex concentrate (PCC) or andexanet alfa may be used to reverse the anticoagulant effect of apixaban. If major bleeding occurs in the setting of an overdose of warfarin, fresh frozen plasma, PCC, or vitamin K may be used to reverse the anticoagulant effect of warfarin.

In the event of an overdose of apixaban or warfarin, the investigator should closely monitor the participant for bleeding.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's Coordinating Investigator based on the clinical evaluation of the participant.

8 Statistical Considerations

8.1 Statistical Hypotheses

The primary efficacy outcome is the composite of valve thrombosis and valve-related thromboembolism. Assuming that time-to-event for the primary efficacy outcome is approximately exponentially distributed (ie, a constant hazard), the first co-primary analysis is to determine whether the hazard rate of the device using apixaban (test) is non-inferior to the hazard rate of the device using warfarin (control) by the margin of 1.75%/ pt-yr. The hypothesis statement is as follows:

$$H_0: \lambda_{apixaban} - \lambda_{warfarin} \geq 1.75\%/pt\text{-}yr$$
$$H_A: \lambda_{apixaban} - \lambda_{warfarin} < 1.75\%/pt\text{-}yr,$$

where λ is the hazard rate of the primary efficacy outcome. The second co-primary analysis is to compare the hazard rate for the apixaban arm to two times the OPC for thromboembolism and valve thrombosis or 3.4%/pt-yr (= 2×1.7%/pt-yr). (**Error! Not a valid bookmark self-reference.** et al., 2014)

Once non-inferiority has been met, we will test the hypothesis that the hazard rate of the device using apixaban (test) is superior to the hazard rate of the device using warfarin (control) for the primary efficacy outcome.

For major bleeding (primary safety outcome), the hypothesis test is to determine whether the hazard rate of the device using apixaban (test) is superior to the hazard rate of the device using warfarin (control). The hypothesis statement is as follows:

$$H_0: \lambda_{apixaban} - \lambda_{warfarin} \geq 0$$
$$H_A: \lambda_{apixaban} - \lambda_{warfarin} < 0,$$

where λ is the hazard rate of the primary safety outcome.

8.2 Sample Size Determination

Approximately 1000 participants will be randomly assigned to study intervention for an estimated total of 500 participants per intervention group with one-sided alpha of 2.5% and an approximate power of 90%. Since the OPC test does not require a statistical significance level, this study is powered for the NI test.

The assumed primary outcome rate is 1.75%/pt-yr with warfarin based on a review of literature available with the On-X aortic devices (Puskas et al., 2018; Tossios et al., 2007; On-X Original PMA #P000037, 2001; McNicholas et al., 2006; Chambers et al., 2013; and Wu et al., 2006). It was assumed that all historical trials enrolled a mixture of high and low risk population (HRP and LRP), but only the PROACT clinical trial (Puskas et al., 2014; Puskas et al., 2018) reported the proportion of high and low risk populations (65% and 35% respectively), which was taken into account to estimate the primary outcome rate for the trial.

The thromboembolism (TE), thrombosis and valve-related mortality (VRM) rates are coincident to the remaining events in the composite. Thus, the sample size will be based on a composite of TE, thrombosis and VRM rates. Except for the PROACT clinical trial data, the publications report the non-hierarchical event rate for VRM and TE. If a participant died due to a TE, it would be counted in both the VRM and the TE rate. The trial by Tossios et al., 2007 report the number of deaths related to TE (n=5) and all valve-related deaths (n=19). The percent of deaths due TE is 26%. It was assumed that for any publication that did not report the number of deaths related to TE that 26% of the deaths were due to TE. Thus, the VRM rates are reduced by 26%.

Table 3 (see section 11) summarizes the available literature, the event rates and their variances. Since the number of historical trials to estimate the event rate in warfarin arm is not large, the Hartung-Knapp-Sidik-Jonkman (HKSJ) method was used to produce more robust estimates of variance of the event rate (IntHout et al., 2014). The pooled event rate of warfarin was estimated as 1.75%/pt-yr with a 95% confidence interval of 1.09%/pt-yr and 2.81%/pt-yr by a random effects HKSJ meta-analysis model with the R metafor package. We project that there will be a similar event rate with apixaban and set the non-inferiority margin for this study at 1.75%/pt-yr, equivalent to a doubling of the estimated event rate in warfarin arm.

To confirm that the non-inferiority margin preserves the treatment effect, we would need to estimate the treatment effect for the use of warfarin post-implantation as compared to placebo. There are no placebo-controlled trials of warfarin for patients with AVR. In the PROACT trial that randomized low risk AVR patients to warfarin (INR 2.0-3.0) or dual antiplatelet therapy (DAPT), the warfarin arm had a hazard rate of 1.15%/pt-yr and the DAPT arm had a hazard rate of 7.02%/pt-yr (detailed in Section 11, Table 4). Given the substantially higher event rate in the DAPT versus warfarin arm, we have conservatively assumed that DAPT was a placebo equivalent. Though not ideal, the treatment effect calculated from this data will be conservative (i.e., smaller) than the treatment effect estimated from a true placebo arm. However, the trial involving DAPT enrolled only low risk AVR patients (i.e., no chronic atrial fibrillation, left ventricular ejection fraction > 30 %, left atrium < 50mm diameter, no spontaneous echo contrasts in the left atrium, no neurological events, no hypercoagulability, and no left or right ventricular aneurysm).

To extrapolate these results to an all-comer AVR population, we employed a conversion factor. The event rate for warfarin in the low risk population is 1.15%/pt-yr, the meta-analysis above demonstrated a pooled event rate of 1.75%/pt-yr for warfarin-treated patients (INR 2.0-3.0), therefore the conversion factor was calculated to be 1.52 (= 1.75/1.15). The number of observed events (95% CI) with 26% reduction to VRM for TE overlap of DAPT in the low risk population is 20.2 (13.00, 30.89) using the Poisson distribution, which translated to an event rate (95% CI) of DAPT arm of 7.02% (4.51%/pt-yr, 10.72%/pt-yr). Multiplying by the conversion factor of 1.52, the DAPT event rate (95% CI) in an all-comer AVR population is 10.65%/pt-yr (6.85%/pt-yr, 16.28%/pt-yr).

Table 2 presents the estimated event rates and confidence intervals for warfarin, DAPT and apixaban in all-comer AVR population. Even if an event rate in apixaban arm is 5%/pt-yr, which is unlikely, the estimated upper 95% CI of the apixaban arm will still remain below the lower 95% CI of the event rate of DAPT.

Table 2. Event rates and confidence intervals for warfarin, DAPT, and apixaban in all-comer AVR population.

Treatment in all-comer AVR population	Event rate (%/pt-yr)	Lower 95% CI (%/pt-yr)	Upper 95% CI (%/pt-yr)
Warfarin*	1.75%	1.09%	2.81%
DAPT†	10.65%	6.85%	16.28%
Apixaban†	1.00%	0.52%	1.66%
	1.25%	0.71%	1.98%
	1.50%	0.90%	2.30%
	1.75%	1.10%	2.60%
	2.00%	1.30%	2.91%
	2.25%	1.50%	3.21%
	2.50%	1.71%	3.51%
	3.00%	2.13%	4.10%
	4.00%	2.98%	5.27%
	5.00%	3.86%	6.42%

* The confidence interval was estimated using the random effects HKSJ meta-analysis model; † The confidence intervals were estimated using Poisson distribution.

Assuming that the event rates for warfarin and apixaban would be similar, a conservative estimate of the treatment effect is 4.04%/pt-yr, which reflects the difference between the upper bound of the 95% CI of the pooled event rate of warfarin (2.81%/pt-yr) and the lower bound of the 95% CI of the event rate in DAPT (6.85%/pt-yr). The non-inferiority margin of 1.75%/pt-yr is approximately 43% (1.75/4.04) of the treatment effect and below ½ of the treatment effect as cited in the 2016 FDA guidance "Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry" (CDER/FDA, 2016).

With an accrual time of 1 year, an assumption that 50% of the expected number of participants will be enrolled in about 5 months (40% of the total accrual time), and a minimum follow-up period of 2 years, the assumed loss to follow-up rate for the period of 2 years is 5%, which is equivalent to a loss hazard rate of 0.026 for both the test and control groups. ***Assuming a one-sided alpha of 2.5%, an approximate power of 90%, an equal event rate of 1.75%/pt-yr in both warfarin and apixaban arms, and an absolute NI margin of 1.75%/pt-yr, the estimated sample size is 990, therefore this study will recruit approximately 1000 participants.***

The major bleeding hazard rate for the control group is assumed to equal 3.63%/pt-yr (Puskas et al., 2018). The reference value was calculated by summing up numbers of events and follow-up years from both high and low risk controls. Using the proposed sample size of 1000, a superiority test for major bleeding has 90% power to detect a difference of 2.13%/pt-yr (i.e., 3.63%/pt-yr for warfarin arm and 1.5%/pt-yr for apixaban arm).

All sample size calculations were done via PASS 16.0.5 (released May, 2019) using Non-Inferiority and Inequality Tests for the Difference of Two Hazard Rates Assuming an Exponential Model for the primary efficacy outcome and Tests for the Difference of Two Hazard Rates Assuming an Exponential Model for the primary safety outcome.

8.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-treat (ITT)	All participants who are randomly assigned to study intervention, regardless of treatment discontinuation or switching, will be included in the ITT population.
On treatment	Participants will be censored 1 week after anticoagulant switching or discontinuation of the assigned treatment; ie, all events occurring within 7 days after anticoagulant change (day 1 is first changed dose or time due for next dose) will be attributed to the randomized group and all events occurring > 7 days will be censored. Participants who took the assigned treatment will be included in the corresponding treatment group until they switch or discontinue as above.
As treated (AT)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they initially received.

8.4 Statistical Analyses

The statistical analysis plan will be developed and approved before the first participant is enrolled and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary outcomes.

8.4.1 Efficacy Analyses

Outcome	Statistical Analysis Methods
Primary	A linearized event rate for each treatment group will be calculated as percentage per patient-year using the ITT population and used for the co-primary analyses. For the first co-primary analysis, if the upper bound of 95% confidence interval of the difference of event rates is less than the non-inferiority margin of 1.75%/pt-yr, it will be concluded that apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for the primary efficacy outcome in participants with an On-X mechanical heart valve implanted in the aortic position. For the second co-primary analysis, if the apixaban arm achieves at least 800 patient-years and the linearized event rate for the apixaban arm is less than two times the OPC (3.4%/pt-yr), the OPC test is passed. (Wu et al., 2014) Once both co-primary analyses are met using the ITT population, we declare success and that apixaban is a reasonable alternative to warfarin for thromboembolic event prevention in this population. If a non-inferiority for the primary efficacy outcome is established, a superior test for the primary efficacy outcome will be performed as follows; if the upper bound of the 95% CI is less than zero, it will be concluded that apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the primary efficacy outcome in participants with an On-X mechanical heart valve implanted in the aortic position.
Secondary	For the individual components of the primary efficacy outcome as secondary outcomes, a linearized event rate for each treatment group and the 95% CI for the difference of linearized event rates will be calculated. The ITT population will be used. Statistical testing will be considered exploratory.

8.4.2 Safety Analyses

All safety analyses will be performed on the AT Population.

Outcome	Statistical Analysis Methods
Primary	Major bleeding as a primary safety outcome will be tested for a superiority using a log-rank test with a one-sided significance level of 0.025. A linearized event rate of major bleeding for both warfarin and apixaban arms will be compared with two times the major hemorrhage OPC, or 0.032/pt-yr (=3.2%/pt-yr). (Wu et al., 2014)
Secondary	All secondary bleeding definitions and clinical events cases defined in Section 7 will be summarized with frequencies and percentages per treatment group.

8.4.3 Other Analyses

As sensitivity analyses, the non-inferiority hypothesis for the primary efficacy outcome will be tested using the NI margin of 1.75%/pt-yr and the On treatment and AT populations and using a Cox proportional hazard regression model with a hazard ratio of 2 for the NI margin and the ITT population.

There are no guideline or consensus definitions of aortic valve replacement patients who are at high risk of valve thrombosis or valve-related thromboembolism. Subgroup analyses for the primary efficacy outcome will stratify by age, race, sex, conduit type, time from surgery, valve size, baseline apixaban dose, and post-randomization time in therapeutic range. We will perform an additional subgroup analysis stratified by risk, with high-risk patients defined as having any of the following: atrial fibrillation, left ventricular ejection fraction < 30%, left atrial dimension >50mm, significant vascular disease, and history of neurological events within 1 year, as utilized in the PROACT trial (Puskas et al., 2018).

No interim analysis for efficacy or futility is planned. The trial will be completed as planned, unless there is a safety issue that warrants modifying or stopping the trial.

9 Supporting Documentation and Operational Considerations

9.1 Regulatory, Ethical, and Study Oversight Considerations

9.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

9.1.2 Financial Disclosure

- Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- HIPAA: Data collected during the study enables investigators to answer the scientific questions for which the study was designed, to ensure that the study has been done properly, and use the information to prepare reports or publications of the study results. The investigators and study sponsor may use the information to report adverse events to regulatory agencies, such as the FDA. Investigators and study sponsor may also transfer the information to contracted partners to provide study-related services; or re-analyze the data from this study in the future or combine it with data from other studies for analysis. Other than as described above, protected health information will not be shared beyond the study investigators and sponsor.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

9.2 Data Protection

- This protocol is a confidential communication of CryoLife. Acceptance of this document constitutes the agreement by the recipient that no unpublished information contained within will be published or disclosed without prior written approval, except that this document may be disclosed to the IRB under the condition that it is requested that they keep it confidential.
- The privacy of participants who participate in this study will be protected by all reasonable means. The Principal Investigator is responsible for study records at study sites. Access to study records, and especially participant information, will be limited to the Investigator, the Sponsor and its representatives, and Regulating Bodies.
- All participant data will remain confidential. Participant names, social security number, address, or any other identifying information will not be reported. Participants and their data will be collected with a unique Participant Number.
- The site staff will be provided with a participant log that they will use to record the unique participant numbers and participant information at the time of each screening. The site staff are responsible for maintaining the log. The unique 6-digit Participant identification number will be assigned according to the following scheme: the first three digits are the site-assigned abbreviation, followed by the sequential number in which the participant was consented (starting with 001).

9.3 Data Quality Control and Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing data surveillance to discern trends and outliers in the data. On-site visits will be performed to ensure that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained for a period of 2 years following the date the marketing application is approved for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified (§312.62(c)). No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.4 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Correspondence regarding a study participant memorandum sent to IRB(s).

9.5 Study and Site Closure

- The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- Reasons for the early closure of a study site by the sponsor may include, but are not limited to:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the investigator
  - Discontinuation of further study intervention development

9.6 Publication Policy

- The results of the study will be presented and published in a timely fashion after the results are available. The publications process for the primary and for all secondary analyses will be overseen by the Steering Committee as outlined in the Steering Committee Charter. Interested participating investigators will have access to the clinical trial data through this publications process. CryoLife reserves the right to future discussions with the Steering Committee including, but not limited to, continuance of current study and/or combining the study data with other data with the intent of publishing a multi-center evaluation.
- The study will be registered on https://www.clinicaltrials.gov.

9.7 Clinical Laboratory Tests

Hemoglobin and serum creatinine tests will be performed by the local laboratory, and all results must be entered into the eCRF. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

9.8 Contraceptive Guidance and Collection of Pregnancy Information

9.8.1 Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

9.8.2 Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Participants randomized to apixaban will return to warfarin anticoagulation for the duration of the pregnancy, with management, including warfarin dosing and/or discontinuation, at the discretion of study investigator or designee.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be collected, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.1 Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to the sponsor medical devices in use in this study

Medical Device Incident/Effect Definitions
Adverse Device Effect (ADE) • Adverse event related to the use of the On-X medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a use error or intentional misuse. **Unanticipated Adverse Device Effect (UADE)** • An Unanticipated Adverse Device Effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

10.2 Documentation of Medical Device Incidents/Effects

Medical Device Incident/Effect Documenting and Reporting
• Any medical device incident/effect occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate valve function form of the eCRF. • For incidents fulfilling the definition of an ADE or UADE, the valve function eCRF page will be completed. • The eCRF will be completed as thoroughly as possible • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial ADE or UADE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence. • Investigators are responsible for reporting UADEs to their IRB per local requirements.

11 References for sample size calculation

Table 3. References used to estimate the primary outcome rate of warfarin (%/pt-yr).

Author	Chambers	McNicholas	On-X Original PMA# P000037	PROACT		Tossios	Wu
				High Risk Control	Low Risk Control		
Year	2013	2006	2001	2018		2007	2006
Country	UK, Spain, Greece	USA	Germany, Spain, Greece	US, Canada		Germany	South Africa
Sample size	214	142	184	190	102	264	104
% of total	18%	12%	15%	16%	9%	22%	9%
Mean patient age (yrs)	59.7	58.6	60.2	55.8	52.5	62	39.7
Median Follow-up (yrs)	5.5	4.5*	2.2*	5.7	3.4	3.9	1.8*
Total Follow-up (pt-yr)	1360	659	411.8	1090	343.5	1069.4	172.5
Target INR	2.0-3.0	2.5-3.5	SoC	2.0-3.0	2.0-3.0	2.5-3.5	1.5-2.5
Mean INR	NR	NR	NR	2.5	NR	NR	43% out of range
NR = Not Reported in the manuscript; * Mean follow-up (yrs) was reported;							
Number of events							
- TE†	8	6	7	19	1	16	2
- Thrombosis	0	0	0	2	0	0	0
- VRM	7	5	1	7	4	19	7
- % TEs in VRM	NR	NR	NR	NR	NR	26%§	NR
Total number of events with 26% reduction to VRM for TE overlap (r)§	13.2	9.7	7.7	30.1#		30.1	7.2
Linearized event rate with 26% Reduction to VRM for TE overlap (λ)§	0.97%	1.47%	1.88%	2.10%#		2.81%	4.16%
Standard error of linearized event rate‡	0.0027	0.0047	0.0068	0.0038		0.0051	0.0155

† Peripheral TE was included if provided; § A 26% VRM was assumed to be related to TE event; # calculated by summing up numbers of events and follow-up years from both high and low risk controls; ‡ calculated as $\lambda/\sqrt{r}$

Table 4. Estimated event rates of standard warfarin and DAPT for low risk patients in the PROACT trial.

	Standard Warfarin (INR 2.0-3.0)	DAPT
Total Follow-up (pt-yr)	343.5 pt-yr	288.1 pt-yr
Sample size	102	99
Number of all TE	1	14
Number of thrombosis	0	4
Number of VRM	4	3
Total number of events with 26% reduction to VRM for TE overlap	4.0	20.2
Linearized event rate with 26% Reduction to VRM for TE overlap	1.15%	7.02%

12 Abbreviations

Abbreviation	Definition
AAP	ascending aortic prosthesis
AVR	Aortic valve replacement
ADE	adverse device effect
AE	adverse event
AT	as treated
BID	twice daily
CDER	Center for Drug Evaluation and Research
CIOMS	Council for International Organizations of Medical Sciences
CMI	Carbomedics
DAPT	dual antiplatelet therapy
DOAC	direct oral anticoagulant
DSMB	data safety monitoring board
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	institutional ethics committee
INR	international normalized ratio (for anticoagulant monitoring)
IRB	Institutional Review Board
ITT	intent to treat

Abbreviation	Definition
HRP	high-risk population
LRP	low-risk population
OPC	objective performance criteria
PCC	prothrombin complex concentrate
PROACT	prospective randomized on-x valve anticoagulation clinical trial
PTFE	polytetrafluoroethylene
pt-yr	patient-year
SAE	serious adverse event
SJM	Saint Jude Medical
SoA	schedule of activities
TE	thromboembolic
UADE	unanticipated adverse device effect
VRM	valve-related mortality
WOCBP	woman of childbearing potential

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A prospective, randomized, active (warfarin) controlled, parallel-arm clinical trial to determine if patients with an On-X aortic valve can be maintained safely and effectively on the factor Xa inhibitor apixaban

(PROACT Xa)

Statistical Analysis Plan

Protocol Version:	1.0
Protocol Date:	January 15, 2020
Analysis Plan Version:	1.0
Analysis Plan Date:	January 15, 2020

Revision History

Version Date	File Name	Summary of Changes

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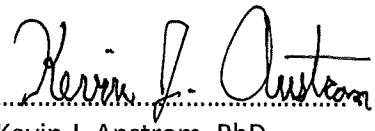

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TABLE OF CONTENTS

Abbreviations

Abbreviation	Definition
AE	Adverse Event
AM	Arithmetic Mean
AT	As Treated
BID	Twice Daily
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
ICF	Informed Consent Form
ICH	International Conference On Harmonization
INR	International Normalized Ratio
ITT	Intent-To-Treat
NI	Non-Inferior
NYHA	New York Heat Association
OT	On Treatment
OPC	Objective Performance Criteria
Pt-yrs	Patient-Years
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
TTR	Time in Therapeutic Range

1 Introduction

PROACT Xa is designed to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained safely and effectively on the factor Xa inhibitor apixaban (Eliquis). The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated participants to updated objective performance criteria (OPC) (Wu et al., 2014) for FDA-approved mechanical heart valves in the aortic position. This is an open-label study in which patients who are at least 3 months out from implantation of an On-X valve in the aortic position will be randomized in a 1:1 fashion to either apixaban 5 mg twice daily (2.5 mg twice daily in selected participants meeting reduced dose criteria) or warfarin adjusted to an INR of 2.0-3.0. Participants will be followed for at least 2 years after randomization with at least 800 patient-years (pt-yrs) of follow-up in each randomized group. If the primary efficacy hypothesis is proven, the data will be used to support a change in the On-X valve device label to state that apixaban is an acceptable alternative to warfarin for anticoagulation in patients 3 or more months after implantation of an On-X valve in the aortic position.

1.1 Study Objectives

1.1.1 Co-Primary Efficacy Objectives

- To determine if apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism
- To determine if apixaban provides acceptable anticoagulation for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism compared with an OPC

1.1.2 Primary Safety Objective

- To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the safety outcome of major bleeding in patients with an On-X mechanical heart valve implanted in the aortic position

1.1.3 Secondary Efficacy Objectives

- To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in patients with an On-X mechanical heart valve implanted in the aortic position
- To compare apixaban with warfarin (INR target range 2.0 – 3.0) for the individual components of the primary outcome (valve thrombosis and valve-related thromboembolism) in patients with an On-X mechanical heart valve implanted in the aortic position

- To compare apixaban with warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in pre-specified subgroups of patients with an On-X mechanical heart valve implanted in the aortic position

1.2 Study Design

This is a prospective, multicenter, open-label, randomized, active controlled clinical trial to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained safely and effectively on apixaban. The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated participants to updated OPC for FDA-approved mechanical heart valves in the aortic position. Each participant will be followed for at least 2 years and each randomized arm will achieve at least 800 pt-yrs.

The study will consist of approximately 1000 participants (randomized 1:1 with approximately 500 participants in the apixaban arm and 500 participants in the warfarin arm) at a minimum of 3 sites and up to 60 sites in North America, and potentially in Europe and/or Japan, who are 18 years of age or older, at least 3 months out from an On-X aortic valve implantation, and currently managing their anticoagulation with warfarin.

Participants will be randomized to either continue warfarin or switch to apixaban. Participants randomized to apixaban will receive 5 mg twice daily (BID), or apixaban 2.5 mg BID in participants with 2 or 3 of the following characteristics:

- age ≥ 80 years
- weight ≤ 60 kilograms
- creatinine ≥ 1.5 mg/dL (133 micromol/L)

For participants randomized to apixaban, INR testing will be performed on the current warfarin dose with the following algorithm to initiate apixaban:

1. INR < 2; stop warfarin and start apixaban
2. INR 2.0 to 3.0; hold warfarin for 2 days, start apixaban on day 3
3. INR > 3.0 to 4.0; hold warfarin for 4 days, start apixaban on day 5
4. INR > 4.0; hold warfarin for 2 days, recheck INR, refer to steps 1, 2, or 3

The procedures to be performed throughout the study are outlined in the Schedule of Activities in the study protocol (see Section 1.1 of the study protocol).

2 Study Populations

For purposes of analysis, the following populations are defined.

Intent-to-treat (ITT)

All participants who are randomly assigned to study intervention, regardless of treatment discontinuation or switching, will be included in the intent-to-treat (ITT) population.

On treatment (OT)

Participants will be censored 1 week after anticoagulant switching or discontinuation of the assigned treatment; i.e., all events occurring within 7 days after anticoagulant change (day 1 is first changed dose or time due for next dose) will be attributed to the randomized group and all events occurring >7 days will be censored. Participants who took the assigned treatment will be included in the corresponding treatment group until they switch or discontinue as above.

As treated (AT)

All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they initially received. For example, if a participant was randomized to apixaban, took 1 dose of apixaban and then switched to non-study warfarin, this participant will be included in the apixaban arm for the as treated (AT) population.

3 Definitions and Derived Variables

3.1 Valve thrombosis

Value thrombosis is defined as any thrombus not caused by infection attached to or near an implanted On-X valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment other than continued oral anticoagulation. Furthermore, valve thrombus found at autopsy in a participant whose cause of death was not valve related or found at operation for an unrelated indication will also be reported as valve thrombosis (Akins et al., 2008).

3.2 Valve-related thromboembolism

Valve-related thromboembolism is defined as any thromboembolic stroke, thromboembolic transient ischemic attack (TIA), thromboembolic myocardial infarction, or arterial thromboembolism to another organ or limb, occurring after the immediate perioperative period and not associated with infection or intracardiac tumor. The independent CEC committee will determine whether a thromboembolism was related to the On-X valve based on clinical evaluation, surgery, and autopsy data. If the thromboembolism is determined to be of unknown origin after clinical evaluation, surgery, and/or autopsy, the thromboembolism will be conservatively considered to be related to the On-X valve.

3.3 Major bleeding

Major bleeding is defined as any episode of internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion, pericardiocentesis or reoperation. Bleeding will be adjudicated by the CEC Committee. Secondary definitions of bleeding, including Bleeding Academic Research Consortium (BARC) and International Society of Thrombosis and Hemostasis (ISTH) definitions of bleeding, will also be adjudicated.

4 Efficacy Parameters

4.1 Primary Efficacy Outcome

The primary efficacy outcome is the composite of valve thrombosis and valve-related thromboembolism. The primary efficacy outcome will be analyzed using a linearized adverse event rate, measured as percentage per patient-year (%/pt-yr).

4.2 Secondary Efficacy Outcome

The secondary efficacy outcome is the individual components of the primary efficacy outcome of valve thrombosis and valve-related thromboembolism. The secondary efficacy outcome will be analyzed using a linearized adverse event rate, measured as %/pt-yr.

5 Safety Parameters

5.1 Primary Safety Outcome

The primary safety outcome is major bleeding and Kaplan-Meier freedom from bleeding at 2 years will be compared using a log-rank test. Major bleeding will be also analyzed using a linearized adverse event rate, measured as percentage per patient-year (%/pt-yr).

5.2 Secondary Safety Outcome

All secondary bleeding definitions and clinical outcomes defined in Section 7 of the study protocol, including valve thrombosis or dysfunction, stroke or TIA, myocardial infarction, arterial thromboembolism, bleeding, hospitalization and the reason for hospitalization, death and the cause of death, will be collected and be summarized with frequencies and percentages per treatment group.

6 Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Statistical methods will be based on the International Conference on Harmonization (ICH) E9 document "Statistical Principles for Clinical Trials".

For screening, demographic and efficacy outputs, data will be summarized by randomized treatment. Safety outputs will be summarized by actual treatment received.

In summary tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The arithmetic mean (AM), median, 95% confidence interval (CI), standard deviation (SD) and standard error (SE) will be presented to one more decimal place than the original data.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of participants within the population treatment group unless otherwise specified.

For efficacy parameters, treatment groups will be compared by the difference in linearized event rates. The estimate of difference in linearized event rates and its 95% CI be presented in statistical analysis outputs.

All hypothesis testing will be carried out at the 2.5% (1-sided) significance level unless otherwise specified.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

Case report form (CRF) data collected will be presented within data listings. The data listings will be sorted by treatment group, site number, participant number and visit.

The treatment label for all Tables, Listings and Figures will be:

Treatment	Treatment Label for TFLs
Apixaban (5 mg BID or 2.5 mg BID)	Apixaban
Warfarin (INR target range 2.0 - 3.0)	Warfarin
All Treatments	Total

Should any of the statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes will be documented in the clinical study report (CSR), including the rationale for use. These include the transformation of the data (for example to a logarithmic scale) in order to satisfy the model assumptions such as normally distributed residuals with constant variance; or the application of non-parametric techniques.

Additional ad-hoc analyses may be conducted as deemed appropriate.

All statistical analysis will be performed using SAS® v9.4 (Cary, NC USA) or higher.

6.1.2 End of study

The end of study is defined as that time when the last participant has been followed for 2 years (that participant's 24 month visit). At that time, the study will end and all participants in the apixaban arm will be transitioned to medically prescribed warfarin, as described in Section 5.8 of the study protocol. Because each participant will have a protocol-mandated final study visit that will be scheduled based on the last participant's 24-month visit, there will not be a definitive study end date because those visits may occur after the last participants 24-month visit. Data analysis will include information collected through each participant's final study visit.

6.1.3 Handling of Dropouts and Missing Data

During the course of the trial, missing data will be monitored by the operations team via system queries in the database and aggregate reports. Participants who are event-free will be censored at their last known alive date (which is typically based on the last non-missing follow-up visit date). If the participant withdraws consent for disclosure of future information, the participant will be censored at the date of a withdrawal of consent.

6.1.4 Determination of Sample Size

With an expected accrual time of 1 year, an assumption that 50% of the expected number of participants will be enrolled in about 5 months (40% of the total accrual time), and a minimum follow-up period of 2 years, the assumed loss to follow-up rate for the period of 2 years is 5%, which is equivalent to a loss hazard rate of 0.026 for both the test and control groups. Assuming one-sided alpha of 2.5%, an approximate power of 90%, an equal event rate of 1.75%/pt-yr in both warfarin and apixaban arms, and an absolute NI margin of 1.75%/pt-yr, the estimated sample size is 990, therefore this study will recruit approximately 1000 participants. Refer to Section 8.2 of the study protocol for the full sample size calculation and the NI margin justification.

As noted in Table 1 showing the expected statistical power based on observed event rates with 1000 participants, the power to rule out an absolute difference of 1.75%/pt-yr or a hazard ratio of 2 is greater than 70% for all scenarios where the event rates for the warfarin and apixaban arms are less than 2.8%/pt-yr. Based on historical trials with warfarin anticoagulation and the On-X valve, the hazard rate in warfarin arm is expected to be ≤2.8%/pt-yr. However, recognizing the uncertainty regarding the background event rate in warfarin arm, the study is designed to have the co-primary analysis with the NI and OPC tests as described in Section 1.2 of this document. Also, as a sensitivity analysis, a proportional hazard regression model with a hazard ratio of 2 for the NI margin will be performed.

Table 1. Expected statistical power by event rate and statistical method with 1000 participants

Event rate in warfarin arm (%/pt-yr)	Event rate in apixaban arm (%/pt-yr)	Hazard rate approach with a NI margin of 1.75%/pt-yr	Hazard ratio approach with a NI margin of 2.0
1.00	1.00	99.1%	33.8%
1.25	1.25	97.2%	40.6%
1.50	1.50	94.1%	47.0%
1.75	1.75	90.3%	52.9%
2.00	2.00	86.1%	58.3%
2.25	2.25	81.8%	63.3%
2.50	2.50	77.5%	67.8%
2.80	2.80	72.6%	72.5%
3.00	3.00	69.5%	75.3%
3.50	3.50	62.5%	86.0%
4.00	4.00	56.6%	100.0%
4.50	4.50	51.5%	100.0%
5.00	5.00	47.2%	100.0%

The empirical type I error rate and power were evaluated using Markov chain Monte Carlo simulations with 10,000 iterations per scenario as presented in Table 2. The hypothesis statements are as follows:

$$H_0: \lambda_{apixaban} - \lambda_{warfarin} \geq 1.75\%/\text{pt-yr}$$
$$H_A: \lambda_{apixaban} - \lambda_{warfarin} < 1.75\%/\text{pt-yr},$$

where λ is the hazard rate of the primary efficacy outcome. The type I error rate was calculated as a proportion of rejecting the null hypothesis, i.e., how many times the upper bound of the 95% CI of hazard rate difference is less than the NI margin of 1.75%/pt-yr, when simulated 10,000 iterations under the null hypothesis ($\lambda_{apixaban}$=1.75%/pt-yr and $\lambda_{warfarin}$=3.50%/pt-yr). The empirical power was calculated in the same way when simulated 10,000 iterations under the alternative hypothesis ($\lambda_{apixaban}$=1.75%/pt-yr and $\lambda_{warfarin}$=1.75%/pt-yr).

Table 2. Simulation results with 1000 participants (90% power)

Simulation scenario	Hazard rate in warfarin (%/pt-yr)	Hazard rate in apixaban (%/pt-yr)	Rate of passing NI test*
Under the alternative hypothesis (Power)	1.75	1.75	89.4%
Under the null hypothesis (Type I error)	1.75	3.50	2.7%

* The data were simulated 10,000 iterations.

6.2 Participant Characteristics

6.2.1 Participant Disposition

The participant disposition table will summarize the following and will be presented for all participants by treatment group and overall.

- The number (%) of participants randomized at the screening visit
- The number (%) of participants withdrawn before the end of study
- The number (%) of participants who completed the study
- The number (%) of participants who crossed over to other treatment than their assigned treatment
- The number (%) of participants who were lost to follow-up
- The number (%) of participants in the ITT population
- The number (%) of participants in the OT population
- The number (%) of participants in the AT population

6.2.2 Baseline Characteristics

Demographic data presented will be age, race and gender. Etiology, lesion, time from surgery and New York Heat Association (NYHA) functional class at screening will be presented as background data. Demographic and background data will be summarized using summary statistics for continuous variables (number of participants, mean, standard deviation, median, minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate. These data will be presented for all three populations (ITT, OT, and AT).

6.2.3 Treatment Exposure and Compliance

For participants randomized to apixaban, participant compliance with the study intervention will be assessed by filling of the drug with a gap in filled supply >14 days defined as non-compliance. For participants randomized to warfarin, participant compliance with the study intervention will be assessed by INR levels. The number (%) of compliant and noncompliant participants will be summarized using the ITT population.

6.2.4 Concomitant Medications

The number (%) of participants reporting the use of any concomitant medications, and the number of reported concomitant medications will be summarized using the ITT population.

6.2.5 Medical Histories

The number of participants reporting one or more conditions for past medical history will be summarized using counts and percentages. Both prior and concomitant medical conditions summaries will use the ITT population.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variable

The co-primary analysis will be conducted for the primary efficacy outcome using the ITT population.

A linearized event rate per arm is defined as the total number of adjudicated efficacy outcomes divided by the total patient time (years). The approximate 95% CI for the difference of linearized event rates will be calculated as

$$\left(\frac{r_A}{T_A} - \frac{r_W}{T_W}\right) \pm 1.96 \sqrt{\frac{r_A}{T_A^2} + \frac{r_W}{T_W^2}},$$

where subscript *A* and *W* denote the apixaban and warfarin arms, respectively, and *r* is the total number of adjudicated efficacy outcomes, and T is the total patient time (years). (Liu et al. 2006)

As the first co-primary analysis, if the upper bound of the 95% CI for the difference of linearized event rates is less than the non-inferiority margin of 0.0175/pt-yr (=1.75%/pt-yr), it will be concluded that apixaban is non-inferior to warfarin for the primary efficacy outcome in participants with an On-X mechanical heart valve implanted in the aortic position.

As the second co-primary analysis, if the apixaban arm achieves at least 800 pt-yrs and the linearized event rate is less than two times the OPC or 0.034/pt-yr (=3.4%/pt-yr), the OPC test is passed. (Wu et al., 2014)

Once both co-primary analyses are met using the ITT population, we declare success and that apixaban is a reasonable alternative to warfarin for thromboembolic event prevention in this population.

If a non-inferiority for the primary efficacy outcome is established, a superiority test for the primary efficacy outcome will be performed using the ITT population. If the upper bound of the 95% CI for the difference of linearized event rates is less than zero, it will be concluded that apixaban is superior to warfarin for the primary efficacy outcome in participants with an On-X mechanical heart valve implanted in the aortic position.

6.3.2 Secondary Efficacy Variables

For the individual components of the primary efficacy outcome as secondary outcomes, a linearized event rate for each treatment group will be calculated as percentage per patient year, and the 95% CI for the difference of linearized event rates will be estimated as Section 6.3.1 above. The ITT population will be used, and statistical testing will be considered exploratory.

6.4 Safety Analysis

6.4.1 Primary Safety Variable

Major bleeding as a primary safety outcome will be tested for a superiority by a log-rank test with a one-sided significance level of 0.025 using the AT population.

A linearized event rate per arm is calculated as the total number of adjudicated major bleeding divided by the total patient time (years) using the AT population. The major bleeding rate for both warfarin and apixaban arms will be compared with two times the major hemorrhage OPC, or 0.032/pt-yr (=3.2%/pt-yr). (Wu et al., 2014)

6.4.2 Secondary Safety Variables

All secondary bleeding definitions and clinical events cases defined in Section 7 of the study protocol will be summarized with frequencies and percentages per treatment group using the AT population.

6.5 Interim Analysis

No interim analysis for efficacy or futility is planned. The trial will be completed as planned, unless there is a safety issue that warrants modifying or stopping the trial.

6.6 Subgroup Analysis

Subgroup analyses for the primary efficacy outcome will be performed by the following factors at baseline (Day 1 Randomization).

- Age: <= 65 years vs. > 65 years
- Race: white vs. non-white
- Sex: female vs. male
- Conduit type: valve alone vs. valve in a conduit
- Baseline apixaban dose: 5 mg BID vs. 2.5 mg BID
- Time from surgery: <= 1 year vs. > 1 year
- Valve size (mm): <= 21 mm vs. > 21 mm

An additional analysis will be done comparing outcomes by post-randomization time in therapeutic range (TTR) in the warfarin arm as <50%, 50-69%, and ≥ 70%. Details of this analysis will be described in a supplementary analysis plan.

There are no guideline or consensus definitions of aortic valve replacement patients who are at high risk of valve thrombosis or valve-related thromboembolism. An additional subgroup analysis will stratify based on the high-risk criteria utilized in the original PROACT trial (Puskas et al., 2018) with high-risk patients defined as having any of the following: atrial fibrillation, left ventricular ejection fraction < 30%, left atrial dimension >50mm, significant vascular disease, and history of neurological events within 1 year.

For each subgroup factor, the linearized event rates of the primary efficacy outcome for both treatment groups and the 95% CI for the difference of linearized event rates will be estimated as Section 6.3.1 above. The ITT population will be used, and statistical testing will be considered exploratory.

6.7 Sensitivity Analysis

Three sensitivity analyses are planned for the non-inferiority hypothesis of the primary efficacy outcome – using the NI margin of 1.75%/pt-yr and the OT population, using the NI margin of 1.75%/pt-yr and the AT population, and using a Cox proportional hazard regression model with a hazard ratio of 2 for the NI margin and the ITT population.

The superiority hypothesis for the primary safety outcome will be tested using the ITT and OT populations as sensitivity analyses.

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8 References

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A prospective, randomized, active (warfarin) controlled, parallel-arm clinical trial to determine if patients with an On-X aortic valve can be maintained safely and effectively on the factor Xa inhibitor apixaban

(PROACT Xa)

Statistical Analysis Plan

Protocol Version:	1.0
Protocol Date:	January 15, 2020
Analysis Plan Version:	1.4
Analysis Plan Date:	January 11, 2023

Revision History

Version Date	File Name	Summary of Changes
1.0	PROACTXa_SAP_2020 01 15_final_clean	Original
1.1	PROACTXa_SAP_2020 04 16_v1.1	Modified the definition of the On treatment population; added the following: calculation of time in therapeutic range, details of time to event analysis, censoring rules, and assessment of model assumptions; updated the lists of tables, figures and listings
1.2	Final-SAP_2020-12-16_v1.2	Modified censoring dates, calculation of time to event for outcomes, and imputation of partially missing event dates; added the following: a sensitivity analysis for different censoring dates, the calculation of time in therapeutic range of INR before the study
1.3	PROACTXa_SAP_20221027_V1.3	Add analysis for questionnaire; modify end of study.
1.4	PROACTXa_SAP_20230111_V1.4	Modified censoring date for AT population Modified start date for primary safety outcome Modified definitions and derived variables for Quality of Life (EQ-5D-5L) Questionnaire and Duke Anticoagulation Satisfaction Scale (DASS) Modified rules to handle missing value for exploratory analysis

Signature page

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Abbreviations

Abbreviation	Definition
AE	Adverse Event
AM	Arithmetic Mean
AT	As Treated
BID	Twice Daily
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
ICF	Informed Consent Form
ICH	International Conference On Harmonization
INR	International Normalized Ratio
ITT	Intent-To-Treat
NI	Non-Inferior
NYHA	New York Heat Association
OT	On Treatment
OPC	Objective Performance Criteria
Pt-yrs	Patient-Years
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
TTR	Time in Therapeutic Range

1 Introduction

PROACT Xa is designed to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained as safely and effectively on the factor Xa inhibitor apixaban (Eliquis) as on warfarin (target INR 2-3). The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated patients to updated objective performance criteria (OPC)[1] (Wu et al., 2014) for FDA-approved mechanical heart valves in the aortic position. This is an open-label study in which patients who are at least 3 months out from implantation of an On-X valve in the aortic position will be randomized in a 1:1 fashion to either apixaban 5 mg twice daily (2.5 mg twice daily in selected patients meeting reduced dose criteria) or warfarin adjusted to an INR of 2.0-3.0. Patients will be followed for at least 2 years after randomization with at least 800 patient-years (pt-yrs) of follow-up in each randomized group. If the primary efficacy hypothesis is proven, the data will be used to support a change in the On-X valve device label to state that apixaban is an acceptable alternative to warfarin for anticoagulation in patients 3 or more months after implantation of an On-X valve in the aortic position.

1.1 Study Objectives

1.1.1 Co-Primary Efficacy Objectives

- To determine if apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism

- To determine if apixaban provides acceptable anticoagulation for patients with an On-X mechanical heart valve implanted in the aortic position for the primary composite outcome of valve thrombosis and valve-related thromboembolism compared with an OPC

1.1.2 Primary Safety Objective

- To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the safety outcome of major bleeding in patients with an On-X mechanical heart valve implanted in the aortic position

1.1.3 Secondary Efficacy Objectives

- To determine if apixaban is superior to warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in patients with an On-X mechanical heart valve implanted in the aortic position

- To compare apixaban with warfarin (INR target range 2.0 – 3.0) for the individual components of the primary outcome (valve thrombosis and valve-related thromboembolism) in patients with an On-X mechanical heart valve implanted in the aortic position

- To compare apixaban with warfarin (INR target range 2.0 - 3.0) for the primary composite outcome of valve thrombosis and valve-related thromboembolism in pre-specified subgroups of patients with an On-X mechanical heart valve implanted in the aortic position

1.1.4 Exploratory Objectives

- To compare apixaban with warfarin (INR target range 2.0 – 3.0) for health-related quality of life (EQ-5D-5L) in patients with an On-X mechanical heart valve implanted in the aortic position

- To compare apixaban with warfarin (INR target range 2.0 – 3.0) for the anticoagulation satisfaction (DASS) in patients with an On-X mechanical heart valve implanted in the aortic position

1.2 Study Design

This is a prospective, multicenter, open-label, randomized, active controlled clinical trial to determine if patients with an On-X aortic valve, alone or as an On-X Ascending Aortic Prosthesis, can be maintained safely and effectively on apixaban. The primary outcome is a composite rate of valve thrombosis and valve-related thromboembolism, which will be used for co-primary analyses. The first co-primary analysis will determine whether apixaban is non-inferior to warfarin (INR target range 2.0 - 3.0) in patients with an On-X mechanical heart valve implanted in the aortic position. The second co-primary analysis will compare the composite rate for apixaban-treated patients to updated OPC for FDA-approved mechanical heart valves in the aortic position. Each patient will be followed for at least 2 years and each randomized arm will achieve at least 800 pt-yrs.

The study will consist of approximately 1000 patients (randomized 1:1 with approximately 500 patients in the apixaban arm and 500 patients in the warfarin arm) at a minimum of 3 sites and up to 60 sites in North America, and potentially in Europe and/or Japan, who are 18 years of age or older, at least 3 months out from an On-X aortic valve implantation, and currently managing their anticoagulation with warfarin.

Patients will be randomized to either continue warfarin or switch to apixaban. Patients randomized to apixaban will receive 5 mg twice daily (BID), or apixaban 2.5 mg BID in patients with 2 or 3 of the following characteristics:

- age ≥ 80 years
- weight ≤ 60 kilograms
- creatinine ≥ 1.5 mg/dL (133 micromol/L)

For patients randomized to apixaban, INR testing will be performed on the current warfarin dose with the following algorithm to initiate apixaban:

1. INR < 2; stop warfarin and start apixaban

2. INR 2.0 to 3.0; hold warfarin for 2 days, start apixaban on day 3
3. INR > 3.0 to 4.0; hold warfarin for 4 days, start apixaban on day 5
4. INR > 4.0; hold warfarin for 2 days, recheck INR, refer to steps 1, 2, or 3

The procedures to be performed throughout the study are outlined in the Schedule of Activities in the study protocol (see Section 1.1 of the study protocol).

2 Study Populations

For purposes of analysis, the following populations are defined.

Intent-to-treat (ITT)

All patients who are randomly assigned to study intervention, regardless of treatment discontinuation or switching, will be included in the intent-to-treat (ITT) population.

On treatment (OT)

Patients will be censored 1 week after permanent discontinuation of the assigned treatment. All events occurring while on study drug up until 7 days of permanent discontinuation of the assigned treatment will be attributed to the randomized treatment assignment. Any event occurring when not on study drug will not be counted. All events occurring >7 days after permanent discontinuation of study drug will be censored. Patients who took the assigned treatment will be included in the corresponding treatment group until they permanently discontinue assigned treatment.

As treated (AT)

All patients randomly assigned to study intervention and who take at least 1 dose of study intervention. Patients will be analyzed according to the intervention they initially received. For example, if a patient was randomized to apixaban, took 1 dose of apixaban and then switched to non-study warfarin, this patient will be included in the apixaban arm for the as treated (AT) population.

3 Definitions and Derived Variables

3.1 Valve thrombosis

Value thrombosis is defined as any thrombus not caused by infection attached to or near an implanted On-X valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment other than continued oral anticoagulation. Furthermore, valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication will also be reported as valve thrombosis[2] .(Akins et al., 2008)

3.2 Valve-related thromboembolism

Valve-related thromboembolism is defined as any thromboembolic stroke, thromboembolic transient ischemic attack (TIA), thromboembolic myocardial infarction, or arterial thromboembolism to another organ or limb, occurring after the immediate perioperative period and not associated with infection or intracardiac tumor. The independent CEC committee will determine whether a thromboembolism was related to the On-X valve based on clinical evaluation, surgery, and autopsy data. If the thromboembolism is determined to be of unknown origin after clinical evaluation, surgery, and/or autopsy, the thromboembolism will be conservatively considered to be related to the On-X valve.

3.3 Major bleeding

Major bleeding is defined as any episode of internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion, pericardiocentesis or reoperation. Bleeding will be adjudicated by the CEC Committee. Secondary definitions of bleeding, including Bleeding Academic Research Consortium (BARC) and International Society of Thrombosis and Hemostasis (ISTH) definitions of bleeding, will also be adjudicated.

3.4 Quality of Life (EQ-5D-5L) Questionnaire

The survey is collected at Baseline, Month 1, Month 6, Month 12, and Month 24.

EQ-5D-5L questionnaire asks questions that are used to derive 5 subscales: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question has 5 choices for health state ranging from best (“no problems”) to worst. A Each subscale is created by summing up the answers to the questions affiliated with the subscale, ensuring that 1 is assigned to the answer indicating no problems and 5 is assigned to the answer indicating worst problem.

An index-based summary score is created as follows:

a) Each subscale is multiplied by a constant obtained from table 2 of the US Valuation of EQ-5D-%L Health States Using an International Protocol[3] (Simon et al., 2019)
b) After subscales have been multiplied by the constant, the index is derived as follows: 1 – absolute value (sum of subscales multiplied by the constant in step a. Lower summary score represents better quality of life. If any items of those 5 items is missing, the summary score is missing.

The EQ VAS score is a separate question on the EQ-5D-5L that represents health status at the time the questionnaire was filled out (0 indicating worst health one could imagine through 100 indicating best health one can imagine.

Section 6.5 of this document describes the analysis for these measures.

3.5 Duke Anticoagulation Satisfaction Scale (DASS)

The survey is collected at Baseline, Month 1, Month 6, Month 12, and Month 24.

Duke Anticoagulation Satisfaction Scale (DASS)[4] (Samsa et al., 2004) is a 25-items questionnaires to measure the positive and negative impact of anticoagulation, and each item has 7 choices ranging from "not at all" to "very much". The 25-items are unitilized to create 3subscales: hassle, limitation, and positive impact.

Subscales are created by summing answers to the questions below:

Hassle: Answers 1 =not at all through 7 = very much

- How much of a hassle (inconvenience) are the daily tasks of anti-clot treatment
- How much of a hassle (inconvenience) are the occasional tasks of anti-clot treatment? (
- How complicated do you find your anti-clot treatment to be?
- How time-consuming do you find your anti-clot treatment to be?
- How frustrating do you find your anti-clot treatment to be?
- How painful do you find your anti-clot treatment to be?
- Overall, how much of a burden do you find your anti-clot treatment to be?
- Overall, how much has anti-clot treatment had a negative impact on your life?
- Compared with other treatments you have had, how difficult is your anti-clot treatment to manage?

Limitations: Answers 1 =not at all through 7 = very much

- How much does the possibility of bleeding or bruising limit you from taking part in physical activities (for example, housework, gardening, dancing, sports, or anything else you would usually do)?
- How much does the possibility of bleeding or bruising limit you from traveling?
- How much does the possibility of bleeding or bruising limit you from getting the medical care you need (for example, visiting a dentist, chiropractor, or doctor of your choice)?
- How much does the possibility of bleeding or bruising limit your ability to work for pay?
- Overall, how much does the possibility of bleeding or bruising affect your daily life?
- Being on anti-clot treatment may mean changing some of your other habits as well.
- How much does anti-clot treatment limit your choice of food (diet)? (
- How much does anti-clot treatment limit the alcoholic beverages you might wish to drink
- How much does anti-clot treatment limit the over-the-counter medications (for example, aspirin, ibuprofen, vitamins) you might wish to take?
- How much do you worry about bleeding and bruising? QSTESTCD = "DASS0120")

Positive Impact: Answers 7 =not at all through 1 = very much

- Overall, how confident are you about handling your anti-clot treatment
- How well do you feel that you understand the medical reason for your anti-clot treatment?
- How much do you feel reassured because of your anti-clot treatment?
- Overall, how much has anti-clot treatment had a positive impact on your life?
- Overall, how satisfied are you with your anti-clot treatment?
- How likely would you be to recommend this form of anti-clot treatment to someone else with your disease or medical condition?

Total score of DASS is the sum of the subscale scores. The score range is 175 (worst) and 25 (best), and if any item of those 25 items is missing, the total score is missing. Higher DASS total score represents higher negative impact (less satisfaction) of anticoagulation. The DASS was validated with 3 subscales: (1) limitations to daily activities, (2) hassles of anticlot treatment, and (3) positive psychological impact of anticoagulation.

Section 6.5 of this document describes the analysis for these measures.

4 Efficacy Parameters

4.1 Primary Efficacy Outcome

The primary efficacy outcome is the composite of valve thrombosis and valve-related thromboembolism. The primary efficacy outcome will be analyzed using a linearized adverse event rate, measured as percentage per patient-year (%/pt-yr).

4.2 Secondary Efficacy Outcome

The secondary efficacy outcome is the individual components of the primary efficacy outcome of valve thrombosis and valve-related thromboembolism. The secondary efficacy outcome will be analyzed using a linearized adverse event rate, measured as %/pt-yr.

5 Safety Parameters

5.1 Primary Safety Outcome

The primary safety outcome is major bleeding and Kaplan-Meier freedom from bleeding at 2 years will be compared using a log-rank test. Major bleeding will be also analyzed using a linearized adverse event rate, measured as percentage per patient-year (%/pt-yr).

5.2 Secondary Safety Outcome

All secondary bleeding definitions and clinical outcomes defined in Section 7 of the study protocol, including valve thrombosis or dysfunction, stroke or TIA, myocardial infarction, arterial thromboembolism, bleeding, hospitalization and the reason for hospitalization, death and the cause of death, will be collected and be summarized with frequencies and percentages per treatment group.

6 Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 General principles

Statistical methods will be based on the International Conference on Harmonization (ICH) E9 document "Statistical Principles for Clinical Trials". All hypothesis testing will be carried out at the 2.5% (1-sided) significance level unless otherwise specified. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999. All statistical analysis will be performed using SAS® v9.4 or higher (Cary, NC USA).

In summary tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The arithmetic mean (AM), median (Q1, Q3), 95% confidence interval (CI), standard deviation (SD) and standard error (SE) will be presented to one more decimal place than the original data. In the event no meaningful information is available through the aforementioned decimal place, the statistician in consultation with the PI or designee will determine the most relevant number of decimals to display. Summaries of continuous characteristics will be based on non-missing observations.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of patients with non-missing values for the variable within the population treatment group unless otherwise specified. In the event that the summary displayed is for a subcategory ("child") of a main category ("parent"), the denominator for the "child" will be based on the non-missing observations for the "parent" (e.g., Heart Failure (Y/N) is a "parent" question and Heart Failure Functional Class (e.g. Class I) is a "child" question. The denominator for Class I will be number of patients who answered yes/no to the Heart Failure question).

Unless otherwise specified in this document, relative study day is defined as the (assessment date of a measurement – randomization date) if assessment date is prior to randomization date and will be defined as (assessment date of measurement – randomization date) + 1 if assessment date is on/after date of randomization. Using this derivation, the day of randomization will be considered study day 1.

Data displayed by visit will utilize an "analysis visit" which will be derived based on windowing outlined in section 6.1.2.

A baseline value is defined as the most recent assessment taken prior to/on day of randomization. When there is a missing assessment, it will not be imputed, thus, patients are excluded from any changes from baseline analysis for which they have a missing baseline value.

Due to the anticipated small number of events, stratification by site would produce sparse data and therefore, the baseline hazard within each stratum would be poorly estimated with such models. For this reason, sites will be pooled together and all Cox proportional hazards models will be adjusted for age of valve only.

Unless otherwise specified, all Kaplan-Meier rates and Kaplan-Meier curves will be performed only with the treatment group.

Case report form (CRF) data collected will be presented within data listings. The data listings will be sorted by treatment group, site number, patient number and visit.

The treatment label for all Tables, Listings and Figures will be:

Treatment	Treatment Label for TFLs
Apixaban (5 mg BID or 2.5 mg BID)	Apixaban
Warfarin (INR target range 2.0 - 3.0)	Warfarin
All Treatments	All Patients

Should any of the statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes will be documented in the clinical study report (CSR), including the rationale for use. These include the transformation of the data (for example to a logarithmic scale) in order to satisfy the model assumptions such as normally distributed residuals with constant variance; or the application of non-parametric techniques.

Additional ad-hoc analyses may be conducted as deemed appropriate.

6.1.2 Analysis visits

Information displayed "by visit" will utilize analysis visits based on windows as opposed to the visits at which the information was collected, except baseline information. Baseline can be referred to the date of screening or Day 1 Randomization when a patient is randomized (see Section 1.1 of the study protocol). Analysis day for purposes of the visit windows are derived as follows (the reference date is the randomization date and is considered to be day 1):

- If date of information is missing, analysis day cannot be calculated
- If date of information < reference date, analysis day = analysis date – reference date
- If date of information ≥ reference date, analysis day = (analysis date – reference date) + 1

The visit windows will be as follows for EQ5D and Duke Anticoagulation Satisfaction Scale obtained at month 1, 6, 12, and 24.

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Month 1	1 < analysis day ≤ 45	30
Month 6	45 < analysis day ≤ 270	180
Month 12	270 < analysis day ≤ 540	360
Month 24	540 < analysis day ≤ 900	720

6.1.3 End of study

As described in the study protocol (Section 5.8), the original plan for the end of study was defined as that time when the last patient has been followed for 2 years (that patient's 24 month visit). However,

the study has been stopped by the DSMB due to safety concerns, thus the end of study has been modified as 30 days after the last dose of study drug or the end of study date.

6.1.4 Handling of Dropouts and Missing Data

For the assessment of primary hypothesis, missing data relating to the indicator for the valve thrombosis or valve thromboembolic events will not be imputed.

Any partially missing date for an adjudicated or site reported event and for termination dates at the time of database lock will be imputed as follows:

- If the day is missing, then the 1st of the month will be used.
- If missing day and month, then June 1st of provided year will be used.
- If year is missing, no imputation will be performed.

If imputation leads to a date being prior to the randomization date, it will be set to the randomization date. If imputation leads to a date being after end of study date, it will be set to the end of study date.

If study drug initiation dates are partially missed, the randomization date will be used.

If a patient is determined as lost to follow-up at the end of study, most recent date of contact where elements of the outcome of interest were assessed will be used for the last date of study.

6.1.5 Time to event analysis

Unless otherwise specified in this document, time to event for the ITT population will be defined as [event date – randomization date] +1 where event occurs and as [appropriate censoring date based on analytic population – randomization date] +1 where event does not occur.

Time to event for the OT population will be defined as [event date – study drug initiation date] +1 where event occurs prior to/at 7 days after permanent study drug discontinuation and as [appropriate censoring date based on analytic population – study drug initiation date] +1 where event does not occur or occurs greater than 7 days after permanent study drug discontinuation.

Unless otherwise specified in this document, time to event for the AT population will be defined as [event date – study drug initiation date] +1 where event occurs and as [appropriate censoring date based on analytic population – study drug initiation date] +1 where event does not occur.

Treatment differences will be evaluated using a Cox proportional hazards model that includes treatment as an indicator variable and adjusted for age of valve, unless specified otherwise. The Breslow method will be used for handling ties. P-value and CI for the HR will be based on the Wald statistic. In addition, the summary tables of these analyses will include the number (%) of patients with event, Kaplan-Meier rates as well as the 95% CI by treatment monthly from randomization through the maximum follow-up. Competing risks are not taken into account for any of the Cox proportional hazards models. Competing risks may be taken into account as a sensitivity analysis if a considerable number of deaths are observed. Kaplan-Meier curves will be produced through maximum follow up available in the study, with number of patients at risk indicated below the plot at specific times.

6.1.6 Censoring

In this study we expect missing outcome data to be infrequent and every effort will be made to collect all information regarding the primary outcomes through the end of the study, even in those who have discontinued the study treatment.

The censoring date for ITT analyses will be the earliest of the following: 1) most recent date of contact where the hospitalization question was assessed for the primary composite outcome or where all elements of bleeding were assessed for the primary safety outcome, including the date of a withdrawal of consent, and 2) death date (when death is not part of the outcome). Patients without any assessment of the outcome of interest will be censored at randomization.

The censoring date for AT analyses will be the earliest of the following: 1) most recent date of contact where the hospitalization question was assessed for the primary composite outcome or where all elements of bleeding were assessed for the primary safety outcome, including the date of a withdrawal of consent, and 2) death date (when death is not part of the outcome). Patients without any assessment of the outcome of interest will be censored at study drug initiation.

The censoring date for OT analysis will be the earliest of 1) most recent date of contact where the hospitalization question was assessed for the primary composite outcome or where all elements of bleeding were assessed for the primary safety outcome, including the date of a withdrawal of consent, 2) death date (when death is not part of the outcome), and 3) 7 days after the permanent discontinuation of assigned study drug. Patients without any assessment of the outcome of interest will be censored at study drug initiation.

A sensitivity analysis with the more conservative censoring date where all elements of the primary composite outcome were assessed will be performed for all three analysis populations.

6.1.7 Assessment of Model Assumptions

The validity of the proportional hazards assumption made in the sensitivity analysis for the non-inferiority hypothesis of the primary efficacy outcome will be examined using a standard graphical methods such as Schoenfeld residual plots; if the assumption holds, the survival curves should be approximately parallel to each other.

An additional analytical method that includes the supremum test as implemented by using the ASSESS statement in PROC PHREG in SAS version 9.4 or higher may be utilized. A p-value of < 0.05 indicates violation of the proportional hazards assumption.

If there is evidence of non-proportionality, a time dependent covariate will be included in the model to account for this.

6.1.8 Determination of Sample Size

With an expected accrual time of 1 year, an assumption that 50% of the expected number of patients will be enrolled in about 5 months (40% of the total accrual time), and a minimum follow-up period of 2 years, the assumed loss to follow-up rate for the period of 2 years is 5%, which is equivalent to a loss hazard rate of 0.026 for both the test and control groups. Assuming one-sided alpha of 2.5%, an

approximate power of 90%, an equal event rate of 1.75%/pt-yr in both warfarin and apixaban arms, and an absolute NI margin of 1.75%/pt-yr, the estimated sample size is 990, therefore this study will recruit approximately 1000 patients. Refer to Section 8.2 of the study protocol for the full sample size calculation and the NI margin justification.

As noted in Table 1 showing the expected statistical power based on observed event rates with 1000 patients, the power to rule out an absolute difference of 1.75%/pt-yr or a hazard ratio of 2 is greater than 70% for all scenarios where the event rates for the warfarin and apixaban arms are less than 2.8%/pt-yr. Based on historical trials with warfarin anticoagulation and the On-X valve, the hazard rate in warfarin arm is expected to be ≤2.8%/pt-yr. However, recognizing the uncertainty regarding the background event rate in warfarin arm, the study is designed to have the co-primary analysis with the NI and OPC tests as described in Section 1.1.1 of this document. Also, as a sensitivity analysis, a proportional hazard regression model with a hazard ratio of 2 for the NI margin will be performed.

Table 1. Expected statistical power by event rate and statistical method with 1000 patients

Event rate in warfarin arm (%/pt-yr)	Event rate in apixaban arm (%/pt-yr)	Hazard rate approach with a NI margin of 1.75%/pt-yr	Hazard ratio approach with a NI margin of 2.0
1.00	1.00	99.1%	33.8%
1.25	1.25	97.2%	40.6%
1.50	1.50	94.1%	47.0%
1.75	1.75	90.3%	52.9%
2.00	2.00	86.1%	58.3%
2.25	2.25	81.8%	63.3%
2.50	2.50	77.5%	67.8%
2.80	2.80	72.6%	72.5%
3.00	3.00	69.5%	75.3%
3.50	3.50	62.5%	86.0%
4.00	4.00	56.6%	100.0%
4.50	4.50	51.5%	100.0%
5.00	5.00	47.2%	100.0%

The empirical type I error rate and power were evaluated using Markov chain Monte Carlo simulations with 10,000 iterations per scenario as presented in Table 2. The hypothesis statements are as follows:

$$H_0: \lambda_{apixaban} - \lambda_{warfarin} \geq 1.75\%/\text{pt-yr}$$
$$H_A: \lambda_{apixaban} - \lambda_{warfarin} < 1.75\%/\text{pt-yr},$$

where λ is the hazard rate of the primary efficacy outcome. The type I error rate was calculated as a proportion of rejecting the null hypothesis, i.e., how many times the upper bound of the 95% CI of hazard rate difference is less than the NI margin of 1.75%/pt-yr, when simulated 10,000 iterations under the null hypothesis ($\lambda_{apixaban}$=1.75%/pt-yr and $\lambda_{warfarin}$=3.50%/pt-yr). The empirical power was calculated in the same way when simulated 10,000 iterations under the alternative hypothesis ($\lambda_{apixaban}$=1.75%/pt-yr and $\lambda_{warfarin}$=1.75%/pt-yr).

Table 2. Simulation results with 1000 patients (90% power)

Simulation scenario	Hazard rate in warfarin (%/pt-yr)	Hazard rate in apixaban (%/pt-yr)	Rate of passing NI test*
Under the alternative hypothesis (Power)	1.75	1.75	89.4%
Under the null hypothesis (Type I error)	1.75	3.50	2.7%

* The data were simulated 10,000 iterations.

6.2 Patient Characteristics

6.2.1 Patient Disposition

The patient disposition table will summarize the following and will be presented for all patients by treatment group and overall.

- The number (%) of patients withdrawn before the protocol-mandated end of study
- The number (%) of patients who completed the study at the end of study
- The number (%) of patients who followed for a minimum of 2 years
- The number (%) of patients who died during the study follow-up period
- The number (%) of patients who were lost to follow-up
- The number (%) of patients who experienced early discontinuation of their assigned treatment
- The number (%) of patients who were lost to follow-up
- Length of follow-up
- The number (%) of patients in the ITT population
- The number (%) of patients in the OT population
- The number (%) of patients in the AT population

6.2.2 Baseline Characteristics

Demographic data presented will be age, race and gender. Etiology, lesion, time from surgery and New York Heat Association (NYHA) functional class at screening will be presented as background data. Demographic and background data will be summarized using summary statistics for continuous variables (number of patients, mean, standard deviation, median (Q1, Q3), minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate. These data will be presented for the ITT population.

6.2.3 Treatment Exposure and Compliance

For patients randomized to apixaban, patient compliance with the study intervention will be assessed by filling of the drug with a gap in filled supply >14 days defined as non-compliance.

For patients randomized to warfarin, patient compliance with the study intervention will be assessed by time in therapeutic range (TTR) using INR levels. TTR will be determined by Rosendaal's method that

assumes that the INR value between two measurements varies linearly from the first value to the second value[5] . (Rosendaal et al. 1993)

- Let INR_i and INR_{i+1} be the two consecutive INR values
- Let D_i and D_{i+1} be the dates associated with these two consecutive INR values, $[(D_{i+1} - D_i) = k, k>1]$
- Assuming the linear increase or decrease between the two consecutive INR measurements, the unit change per day in INR is $m = (INR_{i+1} - INR_i)/(D_{i+1} - D_i)$
- The estimated INR value for the date after D_i (D_{i+1}) will be $INR_i + (m \times 1)$
- Similarly, the estimated INR value for the date (D_{i+2}) will be $INR_i + (m \times 2)$, etc.; the estimated INR value on the date immediately prior to D_{i+1} will be $INR_i + (m \times (k - 1))$.

Each patient randomized to warfarin will have an INR measurement every day, either actual or by estimation through linear interpolation. Percent time in INR target 2.0-3.0 (i.e. TTR) will be calculated in three ways:

1) 100 × (total number of unique days where estimated or actual INR matches the specified INR regimen) / (total number of unique days from the date of the first INR value prior to/at randomization to the date of the last INR value prior to/at randomization)

2) 100 × (total number of unique days where 2.0 ≤ estimated or actual INR value ≤ 3.0) / (total number of unique days from the date of the first INR value after randomization to the date of the last INR value while on study drug warfarin)

3) 100 × (total number of unique days where 2.0 ≤ estimated or actual INR value ≤ 3.0) / (total number of unique days from the date of the first INR value after randomization to the date of the last INR value while in the study)

The number (%) of compliant and noncompliant patients who took warfarin will be summarized using the ITT population.

6.2.4 Concomitant Medications

All medications will be coded using the most recent version of the WHO Drug dictionary. The number (%) of patients reporting the use of any concomitant medications including non-study warfarin, expect aspirin, and the number of reported concomitant medications will be summarized at randomization and after that by treatment group using the ITT population.

6.2.5 Medical Histories

The number of patients reporting one or more conditions for past medical history will be summarized using counts and percentages. Both prior and concomitant medical conditions summaries will use the ITT population.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variable

The co-primary analysis will be conducted for the primary efficacy outcome using the ITT population.

A linearized event rate per arm is defined as the total number of patients with adjudicated efficacy outcomes divided by the total patient time (years). The approximate 95% CI for the difference of linearized event rates will be calculated as

$$\left(\frac{r_A}{T_A} - \frac{r_W}{T_W}\right) \pm 1.96 \sqrt{\frac{r_A}{T_A^2} + \frac{r_W}{T_W^2}},$$

where subscript *A* and *W* denote the apixaban and warfarin arms, respectively, and *r* is the total number patients with adjudicated efficacy outcomes, and T is the total patient time (years)[6]. (Liu et al. 2006)

As the first co-primary analysis, if the upper bound of the 95% CI for the difference of linearized event rates is less than the non-inferiority margin of 0.0175/pt-yr (=1.75%/pt-yr), it will be concluded that apixaban is non-inferior to warfarin for the primary efficacy outcome in patients with an On-X mechanical heart valve implanted in the aortic position.

As the second co-primary analysis, if the apixaban arm achieves at least 800 pt-yrs and the linearized event rate is less than two times the OPC or 0.034/pt-yr (=3.4%/pt-yr), the OPC test is passed. (Wu et al., 2014)

Once both co-primary analyses are met using the ITT population, we declare success and that apixaban is a reasonable alternative to warfarin for thromboembolic event prevention in this population.

If a non-inferiority for the primary efficacy outcome is established, a superiority test for the primary efficacy outcome will be performed using the ITT population. If the upper bound of the 95% CI for the difference of linearized event rates is less than zero, it will be concluded that apixaban is superior to warfarin for the primary efficacy outcome in patients with an On-X mechanical heart valve implanted in the aortic position.

6.3.2 Secondary Efficacy Variables

For the individual components of the primary efficacy outcome as secondary outcomes, a linearized event rate for each treatment group will be calculated as percentage per patient year, and the 95% CI for the difference of linearized event rates will be estimated as Section 6.3.1 above. The ITT population will be used, and statistical testing will be considered exploratory.

6.4 Safety Analysis

6.4.1 Primary Safety Variable

Major bleeding as a primary safety outcome will be tested for a superiority by a log-rank test with a one-sided significance level of 0.025 using the AT population. Time from the study drug initiation date to the date of first adjudicated major bleeding or censoring will be determined as specified in Section 6.1.6.

A linearized event rate per arm is calculated as the total number of patients with adjudicated major bleeding divided by the total patient time (years) using the AT population. The major bleeding rate for both warfarin and apixaban arms will be compared with two times the major hemorrhage OPC, or 0.032/pt-yr (=3.2%/pt-yr)[1]. (Wu et al., 2014)

6.4.2 Secondary Safety Variables

All secondary bleeding definitions and clinical events cases defined in Section 7 of the study protocol will be summarized with frequencies and percentages per treatment group using the AT population.

6.5 Exploratory Analysis

The total DASS score as well as the 3 subscales (hassle, limitations, and positive impact will be analyzed as described below.

The EQ-5D-5L index, the subscales (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) as well as the EQ VAS score will be analyzed as described below. A repeated-measures mixed-effects model with Baseline score as a covariate will be run for each measure described above. The follow-up time-points responses (Month1, Month6, Month 12, and Month 24) will be included as outcome variables, and time as a fixed-effect variable.

Restricted maximum likelihood estimation will be used to model all available data from each subject without imputing missing values. An unstructured covariance matrix will be used, if the model doesn't converge, then a compound symmetry will be used.

Point estimates for each treatment group and treatment group mean differences (Apixaban - warfarin treatment) with 95% confidence intervals (CIs) will be generated for each time point. Additionally, the treatment effect will be averaged across all follow-up time points. The estimated treatment difference and 95% CIs will be obtained using the ESTIMATE Statement in SAS PROC MIXED. However, if the total missing value is greater than 10%, then descriptive statistics will be presented for the non-missing values by visits and overall.

"Total Missing" is derived as follows:

- Numerator: Number of participants missing measure of interest across visits
- Denominator: Number of participants expected to have the measure of interest across visits (# patients in population * 5 visits). Denominator will not take into account when patients died, were lost to follow-up, or withdrew consent.

6.6 Interim Analysis

No interim analysis for efficacy or futility is planned. The trial will be completed as planned, unless there is a safety issue that warrants modifying or stopping the trial.

6.7 Subgroup Analysis

Subgroup analyses for the primary efficacy outcome will be performed by the following factors at baseline (Day 1 Randomization).

- Age: ≤ 65 years vs. > 65 years
- Race: white vs. non-white
- Sex: female vs. male
- Conduit type: valve alone vs. valve in a conduit
- Baseline apixaban dose: 5 mg BID vs. 2.5 mg BID
- Time from surgery: ≤ 1 year vs. > 1 year
- Valve size (mm): ≤ 21 mm vs. > 21 mm

An additional analysis will be done comparing outcomes by post-randomization TTR in the warfarin arm as <50%, 50-69%, and ≥ 70%. Details of this analysis will be described in a supplementary analysis plan.

There are no guideline or consensus definitions of aortic valve replacement patients who are at high risk of valve thrombosis or valve-related thromboembolism. An additional subgroup analysis will stratify based on the high-risk criteria utilized in the original PROACT trial[7] (Puskas et al., 2018) with high-risk patients defined as having any of the following: atrial fibrillation, left ventricular ejection fraction < 30%, left atrial dimension >50mm, significant vascular disease, and history of neurological events within 1 year.

For each subgroup factor, the linearized event rates of the primary efficacy outcome for both treatment groups and the 95% CI for the difference of linearized event rates will be estimated as Section 6.3.1 above. The ITT population will be used, and statistical testing will be considered exploratory.

6.8 Sensitivity Analysis

Three sensitivity analyses are planned for the non-inferiority hypothesis of the primary efficacy outcome – using the NI margin of 1.75%/pt-yr and the OT population, using the NI margin of 1.75%/pt-yr and the AT population, and using a Cox proportional hazard regression model with a hazard ratio of 2 for the NI margin and the ITT population.

For the sensitivity analysis using a Cox proportional hazard regression model, the proportional hazards assumption will be assessed and time from the randomization date to the date of first adjudicated primary composite outcome or censoring will be determined as specified in Section 6.1.6. As mentioned in Section 6.1.6, a sensitivity analysis will be done for all three analysis populations with the more conservative censoring date where all elements of the primary composite outcome were assessed.

The superiority hypothesis for the primary safety outcome will be tested using the ITT and OT populations as sensitivity analyses. Time to the date of first adjudicated major bleeding or censoring will be determined as specified in Section 6.1.6.

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8 References

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