A multi-national trial of a direct oral anticoagulant in children with cardiac disease: Design and rationale of the *Safety of ApiXaban On Pediatric Heart disease On the preventioN of Embolism* (SAXOPHONE) study

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Anticoagulation in children is problematic for multiple reasons. Currently used anticoagulants have significant disadvantages and may negatively affect quality of life (QOL). This manuscript describes the design, rationale, and methods of a prospective, randomized, open label phase II multi-national clinical trial of a direct oral anticoagulant (DOAC), apixaban, in children and infants with congenital and acquired heart disease. This trial is designed to gather preliminary safety and pharmacokinetics (PK) data, as well as generate data on QOL of individuals taking apixaban compared to the standard of care (SOC) anticoagulants vitamin K antagonists (VKA) or low molecular weight heparin (LMWH). A key issue this trial seeks to address is the practice of using therapeutics tested in adult trials in the pediatric population without robust pediatric safety or efficacy data. Pediatric heart diseases are not common, and specific diagnoses often meet the criteria of a rare disease; thus, statistical efficacy may be difficult to achieve. This trial will provide valuable PK and safety data intended to inform clinical practice for anticoagulation in pediatric heart diseases, a setting in which a fully powered phase III clinical trial is not feasible. A second consideration this trial addresses is that metrics besides efficacy, such as QOL, have not been traditionally used as endpoints in regulated anticoagulation studies yet may add substantial weight to the clinical decision for use of a DOAC in place of VKA or LMWH. This study examines QOL related to both heart disease and anticoagulation among children randomized to either SOC or apixaban. There are considerable strengths and benefits to conducting a clinical trial in pediatric rare disease populations via an industry-academic collaboration. The SAXOPHONE study represents a collaboration between Bristol-Myers Squibb (BMS)/Pfizer Alliance, and the National Heart, Lung, and Blood Institute's (NHLBI) Pediatric Heart Network (PHN) and may be an attractive model for future pediatric drug trials. (Am Heart J 2019;217:52-63.)

Background

Prevention of thromboembolic events in children with cardiac disease remains a significant concern to cardiologists and pediatric specialists.[1,2] This is complicated by the fact that thrombotic rates in this population are not well characterized.[3] Based on two randomized studies in children with congenital heart disease[2,4] and one randomized study in children with venous thromboembolism (VTE) events,[5] thrombosis rates of 2–12% may be expected. In addition, quality of life (QOL) is of significant concern in this population and can markedly affect compliance and morbidity for those children on anticoagulation.[6] While it has not been as extensively studied in children as it has in adults, it is clear from the standpoint of clinical management that QOL declines significantly with long term anticoagulation in children, thus making this an important endpoint to study in clinical trials.[6,7]

A working group convened by NHLBI identified thromboprophylaxis in both the single ventricle patient (pre- and post-Fontan) and for central venous line-related VTE as top priorities for research and interventional studies.[8] They cited a retrospective study in which 25% to

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40% of single ventricle patients had clinically evident thrombosis prior to Fontan.[9] An earlier study had found 11% of all children undergoing surgery for congenital heart disease (CHD) developed clinically evident thrombosis,[10] and in both scenarios, thrombosis was associated with increased mortality and morbidity. Additionally, the working group identified a dearth of pediatric-specific data to support recommendations for treatment of clinically significant thrombosis in children with cardiac disease, and for children with asymptomatic thrombosis on venous access lines.

There are currently no FDA-approved indications for use of anticoagulants in children other than unfractionated heparin and the very recently approved dalteparin sodium (Pfizer)*, and there is very little specific research in children for this problem. Guidelines for the use of anticoagulants in pediatric settings are largely extrapolated from randomized controlled trials in adults, expert opinion, and small observational studies in children.[11,12] VKA have been the mainstay of long-term anticoagulation in children with heart disease, with LMWH being used as an alternative to VKA in specific settings. The use of VKA in children carries a significant burden including difficulty in achieving and maintaining therapeutic anticoagulation levels, difficulty of consistent oral dosing in small children, frequent blood draws, reduced bone density,[13] and interaction with diet and medications,[14] all of which contribute to lowered QOL. LMWH (eg, enoxaparin and sodium dalteparin) requires frequent parenteral injections. Hence, there exists an urgent need for new anticoagulation strategies for children.[15] Recommendations have been put forth for the strategies and essential endpoints for anticoagulation trials in children, which should help to harmonize prospective trials.[16]

Currently, there are five direct oral anticoagulants (DOACs) in clinical use including four factor Xa (FXa) inhibitors (apixaban, edoxaban, betrixaban, and rivaroxaban), and one direct thrombin inhibitor (dabigatran). None of these has FDA approval for use in children.[17] BMS/Pfizer Alliance developed apixaban, which, like other DOACs, has a number of features that make it appealing for use in children: ease of administration with oral formulations instead of injection, lack of dependency on antithrombin, lack of dietary interaction, and the possibility of requiring less monitoring of blood levels. Apixaban has been shown to have low rates of bleeding in adult populations,[18] but no pediatric data are available as of now.

The purpose of this paper is to describe the rationale and trial design of an industry-academic collaboration involving the NHLBI-funded PHN and BMS/Pfizer Alliance in conducting a randomized, multi-national clinical trial of the DOAC, apixaban,[19] in children and infants with heart disease, the SAXOPHONE study. This trial is designed to provide preliminary safety and PK data on the prophylactic use of apixaban versus SOC in the pediatric cardiology population. In addition, the trial will compare QOL for children on SOC anticoagulation versus apixaban. The trial results will be used to support apixaban dosing recommendations in children with heart disease.

Table I. Objectives of SAXOPHONE

Study objectives
• Characterize the safety of apixaban in children with heart disease (primary end-point).
• Measure Apixaban PK/PD (FX by chromogenic assay), and anti-FXa activity.
• Determine the impact on QOL of apixaban vs VKA or LMWH
• Gather data on the efficacy of apixaban for thromboprophylaxis (Exploratory Aim).
○ Determine biomarkers reflecting anticoagulant efficacy or thrombosis risk
○ Determine the effects of apixaban on bone density vs VKA

FX, Factor X; *FXa*, Factor Xa; *LMWH*, low molecular weight heparin; *PK/PD*, Pharmacokinetics/Pharmacodynamics; *QOL*, quality of life; *VKA*, vitamin K antagonist.

Materials and methods

Study overview, trial organization, and support

This study is a prospective, randomized, open-label, phase II, multi-center, multi-national clinical trial. The goal of the study is to generate PK, QOL assessments, biomarker, and exploratory safety and efficacy data to inform clinicians regarding apixaban dosing and management in children with congenital or acquired heart disease requiring chronic prophylactic anticoagulation (Table I). When compared with VKA or subcutaneous LMWH, apixaban is expected to be equivalently safe, and may be associated with better patient- and caregiver-reported QOL measures while on therapy.

The study was conceptualized and designed by a panel of world experts in the field and was led by the NHLBI-funded PHN,[20] in collaboration with investigators at BMS. It is being conducted under the existing Investigational New Drug (IND) Application for apixaban as part of the European Medicines Agency-agreed apixaban pediatric investigation plan (PIP). It will utilize both a centralized Institutional Review Board (Cincinnati Children's Hospital Medical Center) (eight centers), and local IRB review for those centers in the United States that do not rely on a central IRB (eight centers). The use of a centralized IRB is expected to simplify administration of a complex protocol across multiple sites, decrease cost and time to protocol initiation, and standardize procedures across all sites. International sites will use their local ethics boards. An independent Data and Safety Monitoring Board (DSMB) advisory to the NHLBI will monitor the trial for data quality and safety. An Events Adjudication Committee, whose members are blinded to treatment assignment, will adjudicate all events involving thrombosis and bleeding, as well as deaths of any cause, using criteria that were established prior to the study and defined in an adjudication charter.

Figure 1

Countries in which the SAXOPHONE trial has been approved or anticipated for initiation are in green. Countries (#sites) are: USA (16), Australia (1), Austria (1), Brazil (6), Canada (1), Finland (1), Germany (3), Israel (2), Italy (2), Mexico (3), Russia (4), Spain (1), United Kingdom (3).

The study will be overseen by NHLBI, BMS/Pfizer Alliance, and a SAXOPHONE Study Committee consisting of representatives from the United States, European Union, and Australia, with co-chairs for the North American and European sites. The function of the Study Committee will be to provide expertise to BMS regarding use of anticoagulation in children, conduct of pediatric trials, and expertise in congenital heart disease, and to participate in the writing of the study protocol. The committee will provide oversight of the trial, provide rapid communication and advice to the multiple recruiting sites (via the principal investigators), and serve to interface between BMS and trial investigators. The committee will be composed of 5 members: 2 pediatric cardiologists who are within the PHN, one of whom will serve as study co-chair, 1 representative from NHLBI (PHN), who is also a pediatric cardiologist, 1 European pediatric cardiologist who will also serve as study co-chair, and 1 Australian hematologist.

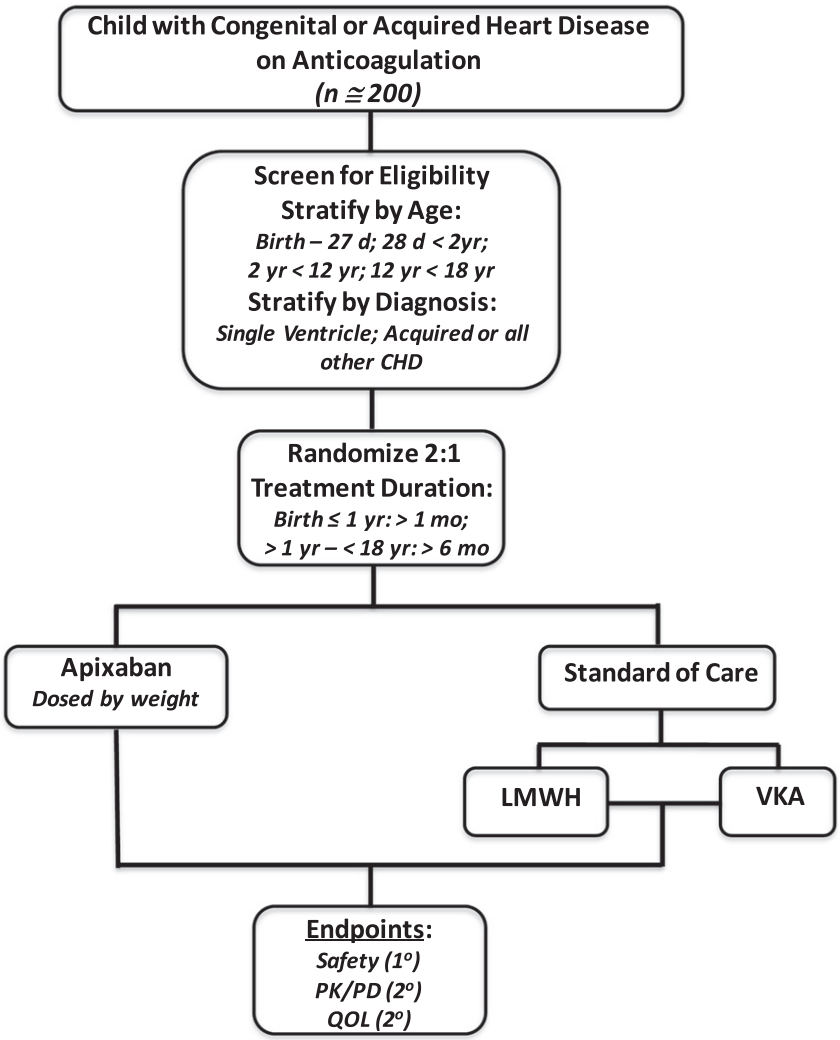
The study will be conducted in 16 North American centers (10 core PHN sites and 6 auxiliary sites), and in 11 countries outside of North America (Figure 1). Enrollment is not capped in US or ex-US sites. All centers will follow the same protocol and study procedures, except that QOL assessments will only be performed in English speaking countries. A total of approximately 200 pediatric participants with congenital or acquired heart disease requiring chronic prophylactic anticoagulation will be randomized 2:1 to apixaban or SOC (VKA or LMWH). Children requiring anticoagulation for treatment of an active thrombotic event or those with mechanical prosthetic valves will be excluded. The structure and design of the SAXOPHONE study is shown in Figure 2.

Support of this trial will come from 2 sources. The NHLBI will fund the infrastructure of the PHN sites via the PHN grants. This includes support for PHN site research coordinators and investigators, and administrative effort and statistical support via the New England Research Institute. BMS/Pfizer alliance will support participant recruitment, drug and supplies, data management, and laboratory measurements. For non-PHN sites, BMS/Pfizer alliance will fund the trial completely. This study is not required by the FDA under the pediatric research equity act (PREA) and is being conducted under the existing IND for apixaban. It is also part of the EMA-agreed apixaban pediatric investigation plan (PIP). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Participant selection

Participant selection criteria will be designed to encourage a heterogeneous group representative of children with heart disease who require long-term anticoagulation for prevention of thromboembolic events. Thus, children with both structural (congenital) heart disease, as well as acquired heart disease will be recruited for the study. The diagnoses of interest will include (but are not limited to) single ventricle

Figure 2



Flow diagram for trial. Participants will be randomized to receive thromboprophylaxis with open label apixaban, or SOC (VKA or LMWH), for up to 12 months or until the need for anticoagulation is resolved. *CHD*, congenital heart disease; *LMWH*, low-molecular-weight heparin; *PK/PD*, pharmacokinetics/pharmacodynamics; *QOL*, quality of life; *SOC*, standard of care; *VKA*, vitamin K antagonist;

congenital heart disease at all stages of palliation, dilated cardiomyopathy, Kawasaki disease with coronary artery aneurysms, and pulmonary hypertension. Eligible participants include those who newly start anticoagulants and those who are currently on VKA or LMWH or other anticoagulants for thromboprophylaxis. Inclusion and exclusion criteria are shown in Table II.

Participants eligible for the study include both males and females, 34 weeks adjusted gestational age to <18 years of age, with congenital or acquired heart disease who are at risk for clot formation which can result in vascular, intracardiac or coronary artery thrombosis, or embolization to other organs or tissue, and who require chronic anticoagulation for thromboprophylaxis under guidelines recommended by the American College of Chest Physicians.[21] To be eligible for the study, participants under age 1 year are expected to require anticoagulation for a minimum of 1 month; whereas participants ≥1 year of age are expected to require anticoagulation for a minimum of 6 months.

Sample size

The reported low incidence of thromboembolic and bleeding events in children limits the feasibility for a

Table II. Inclusion/exclusion criteria

Inclusion	Exclusion
Male and female, 34 weeks adjusted gestational age to <18 yr.	Thromboembolic event less than 6 months prior to enrollment.
Congenital or acquired heart disease requiring anticoagulation for thromboprophylaxis.	Uncontrolled severe hypertension; Gastrointestinal ulcer; Known inherited bleeding disorder or coagulopathy; Active bleeding at time of enrollment; Known intracranial vascular malformation or tumor; Pregnancy.
Subjects eligible if a thrombotic event occurred greater than 6 months prior to enrollment.	Liver dysfunction; Renal function <30% of normal; Platelet count <50,000/μL.
Able to tolerate enteral medications.	Mechanical heart valve.
Aspirin ≤5 mg/kg/day.	ECMO or LVAD at time of enrollment.
Subjects already on anticoagulation for thromboprophylaxis are eligible.	Major bleeding event other than perioperative in prior 3 months.
	Concurrent prophylactic or therapeutic treatment of thrombotic events.
	Anti-platelet therapy, eg, aspirin >5 mg/kg/day.
	Strong inducers / inhibitors of cytochrome P450 3A4 and P-gp.
	Chronic daily use of NSAID's continuously >1 month.
	Current participation in another trial.

ECMO, Extracorporeal membrane oxygenation; *LVAD*, left ventricular assist device; *NSAID*, non-steroidal anti-inflammatory drug.

phase III trial, which would require an excessively high sample size. However, there remains a need to understand the PK profile of apixaban in children with heart disease and gather preliminary data on safety and efficacy that could be used to develop future studies. In this study, PK is intended to serve as a surrogate for efficacy by aiming to achieve apixaban exposure levels in children comparable to those in adults.[22] Due to the anticipated low rates of thromboembolic and bleeding events in the study population and other numerous barriers,[23] a Phase 3 trial powered for efficacy or safety is impracticable.

Because there remains a need to understand the safety and PK/PD profile of apixaban in children with heart disease, the study is designed to obtain apixaban PK, PD, safety information, and exploratory efficacy data. With a treatment period up to 12 months, the sample size of approximately 200 participants is a feasible sample size that will provide a robust PK database and reasonable preliminary safety data along with limited efficacy data in children with heart disease who need chronic thromboprophylaxis. This sample size can be obtained in a reasonable period of time. The observed bleeding events and efficacy data from this study will also provide insight into the expected event rates for the pediatric population on prophylactic apixaban or SOC to inform benefit–risk.

Randomization

Participants will be randomized to receive thromboprophylaxis with open-label apixaban, or SOC (VKA or LMWH), for up to 12 months or until the need for anticoagulation is resolved, whichever occurs first. The study will have a randomization ratio of 2 to 1 for apixaban and comparators, respectively). To ensure even distribution of age and disease types between the two treatment groups, randomization will be stratified by four age groups: birth to 27 days, 28 days to <2 years, 2 to <12 years, and 12 to <18 years. Randomization will also be stratified by clinical diagnosis of single ventricle physiology, and other types of congenital or acquired heart disease. The rationale for the multiple study strata is to ensure that patient groups with differing risks are distributed evenly among the treatment groups. There are no caps on enrollment by age or diagnoses. It is anticipated that this randomization strategy will provide PK and safety data for multiple ages and diagnoses.

Intermittent parenteral anti-coagulation (eg, unfractionated heparin [UFH], LMWH) will be allowed in the apixaban arm when participants cannot tolerate oral intake. In the event of surgical or invasive procedures, apixaban treatment will be held at least 24 hours prior to the procedure and will be resumed no sooner than 24 hours and no later than 10 days after the procedure. Bridging of VKA and LMWH around procedures will be done via local SOC. Participants who receive LMWH are allowed to switch to VKA at any time during the study and conversely, participants having difficulty with VKA may switch to LMWH. Participants will be transitioned to SOC prophylactic anticoagulation at the end of the study and followed for an additional 2 months to capture any clinical events that occur after discontinuation of study drug.

Dose selection

Apixaban doses for the SAXOPHONE study are targeted to achieve a plasma exposure that is similar to the exposure in the adult trial, ARISTOTLE.[18] In this Phase 3 stroke prevention trial in adult patients with non-valvular atrial fibrillation, apixaban achieved superiority for the pre-specified primary endpoint of stroke and systemic embolism with less major bleeding compared with warfarin. It is expected that achieving a similar plasma exposure will result in a favorable safety and efficacy profile in this pediatric population.

The dose of apixaban in the SAXOPHONE study will be determined by a model-based approach, using a

Table III. Dosing based on weight

Apixaban Doses for Ages 3 Months to< 18 Years*

Weight range	Dose	Apixaban Formulation
≥35 kg	5 mg or 12.5 ml twice daily	5-mg tablets, or 0.4 mg/ml oral solution
<35 to 25 kg	4 mg twice daily	For children <5 years use 0.5-mg tablets only.
<25 to 18 kg	3 mg twice daily	For children ≥5 years use either the 0.5-mg tablets or
<18 to 12 kg	2 mg twice daily	0.4 mg/ml oral solution.
<12 to 9 kg	1.5 mg twice daily	
<9 to 6 kg	1 mg twice daily	

*Note: these pediatric doses will be tested in clinical trials and should not be used in clinical practice.

Table IV. Study Assessments and Procedures

Procedure	-21 to 1D	1D	14D	3 mo	6 mo	9 mo*	12 mo	14 mo
Physical exam, Vital Signs, Weight, Height, BMI	X	X	X	X	X	X	X	
PK sampling and Anti-Xa activity Apixaban only		X			X			
Pregnancy test	X			X	X		X	
CBC, ALT, AST, total and conjugated bilirubin, serum creatinine. INR (VKA) or anti-Xa activity (LMWH) per SOC	X		X	X	X		X	
Bone densitometry by DXA		X					X	
Chromogenic FX Assay Apixaban only		X	X					
Biomarkers all subjects ≥1 year of age		X	X		X			
QOL assessment: PedsQL and KIDCLOT		X	X		X		X	
Adverse Events and concomitant medications assessment		X	X	X	X	X	X	X

ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *BMI*, body mass index; *CBC*, complete blood count; *DXA*, dual-energy x-ray absorptiometry; *FX*, factor X; *QOL*, quality of life; *SOC*, standard of care.
*Subjects <2 years of age have a mandatory in-person visit at 9 months. Subjects ≥2 years of age have the option of an in-person or a phone call visit at 9 mo.

Population Pharmacokinetic (PPK) modeling method. Briefly, a PPK model will be developed using available data from a separate apixaban pediatric PK/PD study in which data is available for children aged 3 months to <18 years (Clinical Trials government identifier NCT01707394, estimated enrollment 44 participants as of April 12, 2016). Apixaban exposure from this earlier study was adequately characterized by a two-compartment disposition model, which incorporated clearance (CL/F) of apixaban in children, as well as age and body weight.

Based on this modeling approach, apixaban doses in the trial will be selected using a fixed-dose, body weight-tiered regimen (Table III). Simulations have predicted that this proposed dosing regimen will achieve a similar median steady-state area-under-the-curve (AUC) in children to that observed in adults in the stroke prevention trial who received apixaban. This same approach to dose selection has been used to identify pediatric doses for two other pediatric studies (both reviewed in[17]): 1) a study exploring the safety and efficacy of apixaban for prevention of VTE during induction chemotherapy in children with newly diagnosed acute lymphoblastic leukemia or lymphoma treated with asparaginase,[24] and 2) a study evaluating apixaban in children requiring anticoagulation for the treatment of VTE events. Based on PPK modeling of younger subjects in the Phase 3 non-valvular atrial fibrillation stroke prevention population, and patients in the VTE treatment population, the median daily steady state exposure of apixaban is approximately 2400 ng*hr./mL in patients receiving the 5 mg BID dosing regimen. Thus, the target exposure used to drive dose selection for this protocol is half this value, which is equal to the steady state exposure over one dosing interval, AUC (TAU), of 1200 ng*hr./mL. The PK goal of the SAXOPHONE study is to validate the selected dose and the existing PPK model.

It is anticipated that as data accumulate in children from the pediatric PK/PD component of this study, the PPK model will be updated to inform dosing for the population that is younger than three months.

Study measurements and follow-up

Baseline data. Basic demographics and safety labs will be collected, and study activities performed as detailed in Table IV. PK sampling and chromogenic Factor ten (FX) assays will be performed on participants randomized to apixaban only, and INR performed on VKA participants randomized to SOC who are on VKA per SOC and FX activity for those who are on LMWH. FX activity will also

Table V. Definition of bleeding events

Major	CRNM
Overt bleeding with a decrease in hemoglobin of at least 20 g/L (ie, 2 g/dL) in a 24-hour period.	Overt bleeding requiring blood products. Not related to primary diagnosis.
Bleeding that requires surgical intervention in an OR suite or radiology.	Requires medical or surgical intervention other than an OR suite.
Bleeding that is intracranial or involves the CNS, retroperitoneal space, or lungs.	
Fatal bleeding.	

CNS, Central nervous system; *CRNM*, clinically relevant non-major; *OR*, operating room.

be assayed in participants randomized to apixaban as a PD biomarker. Safety laboratory tests will be performed at routine intervals.

QOL instruments will be administered to English speaking participants. QOL assessments will consist of PedsQL and the Kids Informed Decrease Complications Learning on Thrombosis (KIDCLOT©) and performed at four intervals across the year including baseline and at the end of the study. PedsQL is a modular instrument for measuring health-related QOL in both healthy children and in children with acute and chronic health conditions. It contains both generic core scales and disease-specific modules, has been validated for use in assessing QOL in children with heart disease,[25] and has been successfully used in previous PHN studies of children with congenital heart disease.[26] KIDCLOT© is an inventory tool specifically developed to assess impact of long-term anticoagulant use on health-related QOL in both children (KIDCLOT-PAC Child-Tween QL) and their caretakers (KIDCLOT-PAC Parent-proxy QL).[27] It has been evaluated and preliminarily validated in children requiring long-term anticoagulation.[6,28]

Bone density will be measured using a Dual Energy X-Ray Absorptiometry (DXA) scan and will be performed in participants ≥5 years of age unless it is contraindicated, or country-specific requirements prohibit this as a research question in children. The scan will be performed both at baseline and at the end of study. However, DXA will not be performed in participants who have not had a baseline DXA.

Multiple exploratory biomarkers which may reflect anticoagulant efficacy or risk of thrombosis will be measured in all participants ≥1 year of age in both apixaban and SOC arms. The limits for volumes of blood drawn for this pediatric study will be based on guidelines from the NIH Clinical Center.[29] Participants <1 year of age will not have blood drawn for exploratory biomarkers such as the chromogenic FX assay and the anti-FX activity.

Adverse events and medications will be assessed at every visit and for 2 months after the trial ends.

Trial outcomes

Primary endpoint. This will be a preliminary safety and PK study. There is no primary efficacy endpoint in this study. The primary safety endpoint, confirmed by independent adjudication, will be a composite of adjudicated major or clinically relevant non-major (CRNM) bleeding events per the Perinatal and Pediatric Hemostasis Subcommittee of International Society on Thrombosis and Hemostasis (ISTH) criteria[30] (Table V). Major bleeding is defined as bleeding which satisfies one or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (ie, 2 g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and/or (iv) bleeding that requires surgical intervention in an operating suite, including interventional radiology. In contrast, CRNM bleeding is defined as bleeding which satisfies one or both of the following criteria: (i) overt bleeding for which blood product is administered and that is not directly attributable to the participant's underlying medical condition; and/or (ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite. If bleeding events occur, they will be treated using local treatment protocols for bleeding, as there is no reversal agent approved for apixaban in pediatrics.

Secondary endpoints. Apixaban PK will be characterized using a population PK approach (Table VI for schedule). A chromogenic FX assay that measures (apparent) FX levels will be used to assess the endogenous FX level at baseline and inhibition of FXa by apixaban. In addition, anti-FX activity, which uses exogenous FX and apixaban calibrators, will be measured in participants receiving apixaban to assess their plasma apixaban levels. Nonlinear mixed effects modeling will be used to estimate population and individual PK parameters (eg, CL/F, Vc/F, Ka) and to explore relationships between these parameters and participant demographics (eg, age, body weight, gender), as well as estimate C_{max}, C_{min}, and AUC (TAU) in each participant. Data from this study may be combined with data from other apixaban pediatric trials. PK/PD (measuring FX using chromogenic assay), anti-FXa activity, as well as exposure-response (E-R) relationships, may be explored.

Safety – will include all minor bleeding, drug discontinuation due to adverse events, intolerability, or bleeding, and all-cause death.

Efficacy. The following will be used to generate exploratory information on efficacy.

Table VI. Sampling schedule for PK, PD, and biomarkers

Procedure	Subjects	Screening Day −21 to Day 1	Day 1[a]	Week 2[b] ± 3 days	Month 3 ± 2 wk	Month6 ± 2 wk[c]	Whole Blood Volume
Serial PK and Anti-FXa activity[c]	Subjects taking Apixaban		4 h (3–8 h)[a]	Predose	2 ± 1 h post dose	Predose	1 mL <1 y/o 2 mL ≥1 y/o Sample for PK and anti-FXa combined
Chromogenic FX[c]	Subjects taking Apixaban		Prior to 1st dose[d] and 4 h (3–8 h)[a]		2 ± 1 h post dose	Predose	1 mL/sample
Biomarkers[b,c,e]	All subjects ≥1 y/o	X		Predose		Predose	Minimum of 2.7 mL /sample

FX, Factor 10; *PD*, pharmacodynamics; *PK*, pharmacokinetics.
a The Day 1 post dose 4 hours sample will be taken 4 hours after the first apixaban dose.
b Biomarker samples will not be obtained from children <1 years of age.
c For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation.
d Sample can be taken any time prior to the first dose of study drug at randomization.
e Biomarkers may include but are not limited to thrombin generation, factor VIII, d-dimer, proteins C and S, and fibrinogen.

1. Any thrombotic event detected by imaging or clinical diagnosis. It is anticipated that participants on apixaban will have fewer thrombotic events or bleeding events requiring a significant change in management when compared with participants on SOC.
2. Impact on QOL for participants and caregivers at four points across the study, including baseline and at the end of the study. It is anticipated that those randomized to apixaban will have higher QOL scores from both participants and care-givers, when compared with those randomized to SOC.
3. Data on bone density across 1 year of therapy will be compared between SOC and apixaban participants >5 years of age. This represents a clinically meaningful endpoint that may add additional information other than bleeding. It is anticipated that participants on apixaban will have no decrease in bone density during the trial whereas participants on SOC may have a significant decrease in bone density across 1 year of time.
4. Exploratory biomarkers that may reflect anticoagulant efficacy or risk of thrombosis (eg, thrombin generation, factor VIII, d-dimer, proteins C and S, and fibrinogen) will be measured in all participants ≥1 year of age in both apixaban and SOC arms.

Adjudication

All bleeding events (including major and CRNM and any other bleeding) and thromboembolic events will be adjudicated by an independent Event Adjudication Committee (EAC). Adjudicated thrombotic events will include intra-cardiac thrombosis, shunt thrombosis, coronary artery thrombus in children with aneurysms from Kawasaki disease, stroke, myocardial infarction, pulmonary embolism, cerebral venous sinus thrombosis, arterial thromboembolism, and deep vein thrombosis. Thromboembolic or bleeding events requiring treatment change, medical intervention, hospitalization or prolongation of hospitalization, and thromboembolic event-related death will be confirmed by independent review of imaging results and event adjudication.

An independent DSMB constituted by the NHLBI will have the responsibility to review safety events and will report back to the Steering Committee which oversees the trial. The Chair of the DSMB, along with the PHN leadership and the Sponsor, will be provided with reports of serious adverse events (SAEs) on a regular basis per regulatory reporting requirements. The DSMB may recommend to NHLBI and BMS/Pfizer Alliance modification or suspension of the trial for safety reasons. In addition, the BMS/Pfizer Alliance safety review committee, which oversees their entire pediatric program, will also review safety events in this trial.

The EAC will be an independent chartered committee constituted by experienced clinicians independent of the Investigators and the Sponsor. The responsibilities of the EAC will be to validate all study endpoints that are central to the accuracy of results and conclusions of the trial. Specifically, the EAC will classify endpoints according to documentation provided by investigators. Adjudicated results will be the basis for the final analyses.

Statistical analysis plan

For the primary safety endpoints, descriptive statistics including event rates, difference of event rates and 95% confidence intervals (CI) will be provided, and relative risk and 95% CI for relative risk will be calculated based on the stratified Mantel-Haenszel method, if applicable. Safety analyses will be based on grouping the participants according to the treatment they actually received (the safety population). Exploratory efficacy analyses will be

based on an intention to treat population. For QOL, it is anticipated there will be a return of approximately 75 QOL surveys from participants with approximately 50 on apixaban and 25 on SOC. This would give 85% power at a level of 0.05 to detect an effect size of 0.7 using a 2-sided *t* test. This is generally considered a large effect size and will be able to detect clear changes in QOL but may not be able to detect subtle differences between populations.

Discussion

The primary outcome from this trial will be preliminary data on safety and to provide PK data for at least 133 children with heart disease on prophylactic apixaban. The trial is not expected to be sufficiently powered to detect differences in either efficacy or safety due to the low incidence of thromboembolic and bleeding events in children. As noted above, thrombotic event rates of 2–12% may be expected. At a power of 85%, alpha of 0.05, and expected event rates of 8% (VKA) and 4% (assuming apixaban is better), this would require 1262 randomized participants to show efficacy, which is not feasible. Prospective trials in pediatric anticoagulation have been difficult to accomplish due to such low event rates, as shown by the REVIVE trial, a primary treatment trial, which closed early due to low patient accrual,[31] and smaller enrollment cohorts such as the ProTekt trial, which was a primary prophylaxis trial.[5] Thus, a phase III efficacy trial in pediatrics is unlikely to be feasible due to the required large sample sizes.

Prophylactic anticoagulation is used in multiple settings for children with heart disease, (eg, Kawasaki disease versus Fontan surgery for single ventricle) and with a wide range in age of the child. By themselves, the numbers of children in any one setting are too small to generate adequate safety information in a reasonable length of time. By including a heterogeneous group of pediatric heart disease lesions, safety data will be obtained for multiple diagnoses and ages, and the larger group will inform on safety events for children with heart disease who require anticoagulation. The 'risk' with this approach is that the numbers of children with specific diagnoses, eg, Kawasaki, may be so small that safety events are not detected. This risk is mitigated in part because all subjects will have blood drawn for PK and thus, drug exposure data will be clearly tracked relative to type of heart disease, which will provide additional safety information.

The pragmatic approach of the SAXOPHONE trial has strong justification. First, few prospective trials of anticoagulation have been performed in children when compared with the robust data in adult populations.[32] The THROMBOTECT trial in children is the largest to date with an enrollment of 949 participants and compared LMWH, antithrombin, and unfractionated heparin in children with acute lymphoblastic leukemia at induction.[33] No previous trial of primary prophylaxis in children with congenital or acquired heart disease has enrolled more than 150 participants.[5] As a result, indications for, and dosing of, anticoagulation are often extrapolated from adult data with little consideration for the different physiology and metabolism in children. Second, management of VKA is difficult in children and requires considerable institutional infrastructure to achieve safe and effective anticoagulation, which may not be available in many centers. Indeed, the consistency of anticoagulation in children on VKA is notoriously difficult. The observed differences in clinical practice are correspondingly large with widely ranging target INR values employed.[34] In addition, diet and higher activity levels in children modulate VKA dosing in unpredictable ways. Use of apixaban in children may resolve some of these difficulties. Thus, it is anticipated that the results of this study will have an impact on the practice of pediatric cardiology through the systematic data provided.

Several key exploratory findings are anticipated from this trial. First, important data on PK will allow estimation of apixaban dose across different age groups in a broad pediatric heart disease population. By aiming to achieve apixaban exposure/plasma levels in children comparable to those in adults, PK data will be used as surrogate for apixaban efficacy in children where only limited clinical outcome data can be generated. The FDA recently published a series of potential surrogate endpoint tables with the intended goal of facilitating drug development.[35] This clinical trial in children, although of relatively small scale, will provide important complementary data since indications for anticoagulant prophylaxis in adults, such as atrial fibrillation, cannot be safely translated to the various indications in children with heart disease. Indeed, prospective clinical trials of medication use in children with heart disease are generally lacking and, as a result, there is wide variation in management of complex patients, such as the Fontan patient.[36]

Secondly, we will compare the impact of apixaban prophylaxis with SOC on bone density across 1 year. Although not expected to provide definitive answers, the findings may lend weight to the discussion of adverse effects of SOC versus apixaban.

Finally, this trial will shed light on one of the most important aspects of anticoagulation from the patient and family viewpoint, QOL, which may impact compliance with the medical regimen. For example, studies have suggested that QOL is substantially lower in children with congenital heart disease[37,38] and impacts key areas of life such as school performance. In addition, the FDA has become more interested in assessing QOL in pediatric clinical trials. A primary tool that will be used in this study to assess QOL is KIDCLOT. Although KIDCLOT is not yet validated by the FDA as a surrogate endpoint, which will be a limitation of this trial, its use in this trial is expected to provide information on the QOL of apixaban versus the SOC in children on anticoagulation. Thus, a strong rationale for examining QOL in this study is that even if safety and efficacy were equal between treatment arms, differences in QOL may favor one treatment.

There are multiple advantages to academic-industry collaborations for clinical trials, especially in pediatrics where many diseases meet criteria for rare or Orphan Disease designation. For example, development of an innovative therapeutic for cystic fibrosis was accelerated by the partnership between academic medical institutions, the pharmaceutical industry, and disease-focused foundations. As noted by Ramsey et al, in the development and approval of ivacaftor for cystic fibrosis,[39] the academic medical institutions provided basic and translational expertise, expertise in clinical disease and trial design, and trial network sites for recruitment; industry provided access to new medications, regulatory support, preclinical and PK studies, funding, and faster trial enrollment via national and international trial development; and disease focused foundations provided funding, clinical trial network support and longitudinal patient registries.

Trials from academic – industry collaborations have resulted in high impact publications with both industry employees and academic investigators involved in trial design and authorship. This reflects the higher level of expertise and rigor in study design and execution. Concerns by academic investigators about these partnerships have included loss of academic freedom and data analysis is often conducted without academic involvement.[40] However, most academic investigators have found the collaborations to be beneficial, with a high percentage of publications having a first author academic. Concerns about intellectual property and ownership of data have not been a significant impediment to collaborative research.[41]

Thromboembolic events in children are rare when compared with those in adults, yet the morbidity of thromboembolism and anticoagulation therapy in children has even greater impact because of their longer lifespan and hence, greater societal and personal cost. In addition, pediatric heart disease is rare when considered by individual diagnoses, such as single ventricle or Kawasaki disease. This makes it difficult to accrue adequate participant numbers to power a prospective trial in a reasonable length of time, especially when only a few centers are involved. For example, similar studies in pediatric anticoagulation in heart disease previously conducted by academic institutions have been stopped early due to slow accrual.[31] Thus, a key advantage of multi-national trials in pediatric anticoagulation regimens include shorter time to completion of enrollment and larger cohorts.

The academic-industry partnership between the NHLBI-sponsored PHN and BMS/Pfizer Alliance brings the power of collaboration between academic investigators with expertise in pediatric heart disease and clinical trial design in pediatrics, together with the pharmaceutical industry with its expertise in organizing international randomized therapeutic trials. This pediatric academic-industry partnership leverages the existing clinical network and scientific experience of the PHN in conducting clinical trials in rare pediatric diseases to efficiently complete a study on an industry-driven timeline. In turn, BMS/Pfizer brings significant value by having international experience to include centers in many countries allowing faster enrollment and increased generalizability of the clinical findings. It is hoped that with completion of this, and other trials of DOAC use in the pediatric population, follow-on prospective studies will be quickly designed to address additional anticoagulation needs in children.

In summary, this trial will generate dosing and preliminary safety data on prophylactic use of apixaban in children with heart disease and provide information on clinically relevant endpoints. It is expected that the SAXOPHONE study will advance our knowledge and understanding of dosing and indications for use of the DOAC, apixaban, in the pediatric cardiology population and inform clinical care.

**Note: After submission of this manuscript, the FDA approved the subcutaneously administered LMWH, dalteparin sodium (Pfizer's Fragmin) on May 16, 2019, to reduce the recurrence of symptomatic VTE in pediatric patients 1 month of age and older.*

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References

1. Giglia TM, Massicotte MP, Tweddell JS, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation 2013;128(24):2622-703.
2. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol 2011;58(6):645-51.
3. Jones S, Butt W, Monagle P, et al. The natural history of asymptomatic central venous catheter-related thrombosis in critically ill children. Blood 2019;133(8):857-66.
4. Wessel DL, Berger F, Li JS, et al. Clopidogrel in infants with systemic-to-pulmonary-artery shunts. N Engl J Med 2013;368(25):2377-84.
5. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. Thromb Res 2003;109(2–3):101-8.
6. Bruce AK, Bauman ME, Jones S, et al. Recommendations for measuring health-related quality of life in children on anticoagulation. J Thromb Haemost 2012;10(12):2596-8.
7. Torok RD, Li JS, Kannankeril PJ, et al. Recommendations to enhance pediatric cardiovascular drug development: report of a multi-stakeholder think tank. J Am Heart Assoc 2018:7(4).
8. McCrindle BW, Li JS, Manlhiot C, et al. Challenges and priorities for research: a report from the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH) Working Group on thrombosis in pediatric cardiology and congenital heart disease. Circulation 2014;130(14):1192-203.
9. Manlhiot C, Brandao LR, Kwok J, et al. Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr 2012;161(3):513-9. e3.
10. Manlhiot C, Menjak IB, Brandao LR, et al. Risk, clinical features, and outcomes of thrombosis associated with pediatric cardiac surgery. Circulation 2011;124(14):1511-9.
11. Goldenberg NA, Takemoto CM, Yee DL, et al. Improving evidence on anticoagulant therapies for venous thromboembolism in children: key challenges and opportunities. Blood 2015;126(24):2541-7.
12. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv 2018;2(22):3292-316.
13. Barnes C, Newall F, Ignjatovic V, et al. Reduced bone density in children on long-term warfarin. Pediatr Res 2005;57(4):578-81.
14. Newall F, Barnes C, Savoia H, et al. Warfarin therapy in children who require long-term total parenteral nutrition. Pediatrics 2003;112(5), e386.
15. Kerlin BA. Current and future management of pediatric venous thromboembolism. Am J Hematol 2012;87(Suppl 1):S68-74.
16. Male C, Monagle P, Chan AK, et al. Recommendations for the development of new anticoagulant drugs for pediatric use: communication from the SSC of the ISTH. J Thromb Haemost 2015;13(3):481-4.
17. von Vajna E, Alam R, So TY. Current clinical trials on the use of direct oral anticoagulants in the pediatric population. Cardiol Ther 2016;5(1):19-41.
18. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
19. Wong PC, Crain EJ, Xin B, et al. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. J Thromb Haemost 2008;6(5):820-9.
20. Mahony L, Sleeper LA, Anderson PA, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27(2):191-8.
21. Guyatt GH, Akl EA, Crowther M, et al. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):7S-47S.
22. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011;128(5):e1242-9.
23. Massicotte MP, Sofronas M. deVeber G. Difficulties in performing clinical trials of antithrombotic therapy in neonates and children. Thromb Res 2006;118(1):153-63.
24. O'Brien SH, Li D, Mitchell LG, et al. PREVAPIX-ALL: Apixaban Compared to Standard of Care for Prevention of Venous Thrombosis in Paediatric Acute Lymphoblastic Leukaemia (ALL)-Rationale and Design. Thromb Haemost 2019;119(5):844-53.
25. Marino BS, Tomlinson RS, Wernovsky G, et al. Validation of the pediatric cardiac quality of life inventory. Pediatrics 2010;126(3):498-508.
26. Sleeper LA, Anderson P, Hsu DT, et al. Design of a large cross-sectional study to facilitate future clinical trials in children with the Fontan palliation. Am Heart J 2006;152(3):427-33.
27. Bauman ME, Black K, Kuhle S, et al. KIDCLOT: the importance of validated educational intervention for optimal long term warfarin management in children. Thromb Res 2009;123(5):707-9.
28. Bruce AA, Bauman ME, Black K, et al. Development and preliminary evaluation of the KIDCLOT PAC QL: a new health-related quality of life measure for pediatric long-term anticoagulation therapy. Thromb Res 2010;126(2):e116-21.
29. Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89(1):46-53.
30. Mitchell LG, Goldenberg NA, Male C, et al. Perinatal and Paediatric Haemostasis Subcommittee of the SSC of the ISTH. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children. J Thromb Haemost 2011;9(9):1856-8.
31. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. Thromb Res 2003;109(2–3):85-92.
32. Dabbous MK, Sakr FR, Malaeb DN. Anticoagulant therapy in pediatrics. J Basic Clin Pharm 2014;5(2):27-33.
33. Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, et al. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica 2019;104(4):756-65.
34. Mahle WT, Simpson SA, Fye P, et al. Management of warfarin in children with heart disease. Pediatr Cardiol 2011;32(8):1115-9.

35. U. S. Food & Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. In: https://wwwfdagov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636htm; 2018.
36. Anderson PA, Breitbart RE, McCrindle BW, et al. The Fontan patient: inconsistencies in medication therapy across seven pediatric heart network centers. Pediatr Cardiol 2010;31(8):1219-28.
37. Uzark K, Jones K, Slusher J, et al. Quality of life in children with heart disease as perceived by children and parents. Pediatrics 2008;121(5):e1060-7.
38. Niemitz M, Gunst DCM, Hovels-Gurich HH, et al. Predictors of health-related quality of life in children with chronic heart disease. Cardiol Young 2017;27(8):1455-64.
39. Ramsey BW, Nepom GT, Lonial S. Academic, foundation, and industry collaboration in finding new therapies. N Engl J Med 2017;376(18):1762-9.
40. Rasmussen K, Bero L, Redberg R, et al. Collaboration between academics and industry in clinical trials: cross sectional study of publications and survey of lead academic authors. BMJ 2018;363:k3654.
41. Silva PJ, Ramos KS. Academic medical centers as innovation ecosystems: evolution of industry partnership models beyond the Bayh-Dole Act. Acad Med 2018;93(8):1135-41.