anticoagulation. When compared with VKA or subcutaneous LMWH, apixaban is expected to be safe, and may improve QOL in the study population.

Objectives:

The objectives of this study are to assess the following in pediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation:

- Primary Objectives
  *the safety of apixaban
- Secondary Objectives
  * apixaban PK, PD (by measuring FX using chromogenic assay), and anti-FXa activity
  *the effects of apixaban versus VKA or LMWH on QOL measures
  *the efficacy of apixaban for thromboprophylaxis (exploratory aim)

[redacted]

Study Design:

[redacted] Recruitment started in January 2017 for children of ages ≥ 2 to < 18 years, and was subsequently expanded to ≥ 3 months in December 2017. Enrollment was further expanded in February 2020 to subjects ages 28 days to < 3 months. Neonates will no longer be included in the study population [redacted].

This will be a prospective, randomized, open-label, Phase II, multi-center clinical trial. Approximately 200 pediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation will be randomized 2:1 to apixaban (targeting approximately 133 subjects) or active comparator (VKA or LMWH, targeting approximately 67 subjects). Randomization will be stratified by three age groups: 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.

Subjects will be randomized to receive thromboprophylaxis with either open-label apixaban or an active comparator (VKA or LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. A month is defined as every 30 days from the date of randomization. Intermittent anti-coagulation (e.g., unfractionated heparin [UFH], LMWH) is allowed in the apixaban arm when patients cannot tolerate oral intake or when bridging around surgeries or procedures. Subjects who receive LMWH are allowed to switch to VKA at any time during the study; and conversely, subjects having difficulty with VKA may switch to LMWH. Each subject will be transitioned to SOC at the completion of the study and followed for 2 additional months.

During the study treatment period, in-person study visits will occur at 2 weeks ± 3 days, 3 months ± 2 weeks, 6 months ± 2 weeks, and 12 months ± 2 weeks. Study visits should be scheduled from a starting point of 'Day 1' in order to ensure that a 12 month treatment duration is achieved. Visits will consist of obtaining and reporting adverse events (including bleeding and secondary endpoints), monitoring medication adherence and laboratory testing. Subjects who are < 2 years of age will have a mandatory in-person visit at 9 months ± 2 weeks to include weight measurement, dose adjustment (if necessary) reporting adverse events, and assessing medication adherence. Subjects who are ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. Subjects aged 28 days to < 3 months at the time of randomization will have an office visit at 6 weeks ± 3 days for assessment of body weight in order to adjust the dose of study medication (if necessary). The phone visit will monitor adverse events and medication adherence. Sparse samples for PK will be taken in subjects receiving apixaban. For all subjects, a follow-up telephone or in person safety assessment will be scheduled at 14 months ± 2 weeks or 2 months ± 2 weeks following cessation of study drug if duration of therapy is less than 12 months.

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single- and repeat-dose studies in mice, rats, dogs, and/or monkeys, in vitro and in vivo genotoxicity studies, carcinogenicity studies in mice and rats, reproductive and developmental studies in mice, rats and rabbits, in vitro hemolytic potential, and juvenile toxicity studies in rats. Findings from these nonclinical studies indicate that apixaban has a very low potential for toxicity and support the clinical use of apixaban in pediatric patients.

Apixaban has been studied extensively in adults for various clinical indications, and it has been granted market authorizations for adult use for prevention and treatment of VTE and for prevention of stroke and systemic embolism in patients with NVAF in the United States, the European Union, Canada, Japan, and many other countries. Safety and efficacy for long term use of apixaban have been demonstrated in several completed pivotal phase 3 studies. These studies are briefly discussed below:

- Treatment of VTE: efficacy and safety of apixaban for the treatment of VTE indication have been demonstrated in 2 completed pivotal Phase 3 studies, AMPLIFY [24] and AMPLIFY-EXT. [25] AMPLIFY was a prospective randomized double-blind trial that compared apixaban (10 mg twice daily for seven days followed by 5 mg twice daily for six months) with conventional anticoagulation (subcutaneous enoxaparin for five days followed by warfarin for six months) in 5395 adult patients for the treatment of acute VTE. This study achieved non-inferiority between the two groups in the standard efficacy endpoints of recurrent symptomatic VTE or VTE-related death. It also demonstrated superiority of apixaban in the safety endpoint of major bleeding. Apixaban was also studied in a randomized, double-blind study (AMPLIFY-EXT study) comparing the efficacy and safety of two doses of apixaban (a thromboprophylactic dose of 2.5 mg twice daily or a therapeutic dose of 5 mg twice daily, both given for 12 months) with placebo in 2482 adult patients with VTE who had completed 6 to 12 months of anticoagulation and for whom there was equipoise regarding the further continuation of anticoagulation. The primary efficacy outcome, symptomatic recurrent VTE or death from any cause, occurred in 11.6, 3.8, and 4.2 percent of those receiving placebo, the 2.5 mg twice daily dose, and the 5 mg twice daily dose, respectively. The primary safety outcome, major bleeding, occurred in 0.5, 0.2, and 0.1 percent of those receiving placebo, the 2.5 mg twice daily dose, and the 5 mg twice daily dose, respectively.
- Prevention of stroke and systemic embolism in NVAF: the efficacy and safety of apixaban for prevention of stroke or systemic embolism in NVAF have been demonstrated in two landmark phase 3 studies, ARISTOTLE[17] and AVERROES.[18] ARISTOTLE evaluated apixaban versus warfarin in 18,201 adult patients with NVAF who were suitable for warfarin therapy, and AVERROES evaluated apixaban versus aspirin in 5,598 adult patients with NVAF who were considered unsuitable for treatment with warfarin. In AVERROES, when compared with aspirin, apixaban reduced stroke by > 50% without a significant increase in major bleeding. In ARISTOTLE, when compared to warfarin, apixaban reduced stroke and systemic embolism by 21%, reduced bleeding by 31% and reduced all-cause mortality by 11%. In both studies, apixaban demonstrated consistent effects among all major subgroups, fewer study drug discontinuations than either comparator, and good tolerability and overall safety.

anticoagulation for a minimum of 1 month; whereas subjects ≥ 2 years of age should be expected to require anticoagulation for a minimum of 6 months, although the full treatment of 12 months is most desirable. Subjects who are expected to be chronically anticoagulated (> 1 year), should have a study treatment duration of 12 months. Subjects who receive LMWH are allowed to switch to VKA at any time during the study; and vice versa. All subjects will be transitioned to the standard of care (SOC) at the end of the study (see Section 4.5.3 for converting from apixaban to other anticoagulants), and will be followed for another 2 months. Study drug diaries will be used to record study drug administration.

There will be 3 study periods extending up to 14 months total. These include a screening/randomization period from Day -21 to Day 1, a treatment period from Day 1 to Month 12 (or when anticoagulation is no longer needed), and a follow-up period from Month 12 to Month 14 (or 2 months following cessation of study drug if the duration of therapy is less than 12 months). A month will be defined as every 30 days from the date of randomization.

The Screening/Randomization Period will occur after consent is obtained and will begin with a screening visit that occurs between 0-21 days prior to randomization. At the screening visit (enrollment) the Interactive Web Response System (IWRS) will be contacted to obtain a unique subject number. A complete medical history, including current medications, and a physical examination including vital signs (heart rate, respiratory rate, blood pressure, and temperature), height, and body weight will be performed. The screening visit laboratory studies will include: [redacted] CBC, ALT, AST, total and conjugated bilirubin, serum creatinine (estimated GFR), INR, aPTT, and serum or urine pregnancy test for women of child bearing potential (WOCBP). WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy). All WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG) within 24 hours prior to the start of study drug. An extension up to 72 hours is permissible in situations where pregnancy test results cannot be obtained within the standard 24 hour window. Screening laboratory studies will be interpreted at each site, not at a central core lab. To avoid unnecessary blood draws, safety labs including CBC, liver and renal function tests, coagulation tests that are run 1 to 7 days prior to consent/screening visit as part of clinical care may be used to satisfy the inclusion/exclusion criteria as long as the investigator believes the lab values could not have changed at enrollment.

The **randomization** visit may occur any time within the 21 day period after the screening visit (enrollment). For subjects who meet all the inclusion/exclusion criteria, the IWRS will be contacted and the subjects will be randomized. The subjects will receive instructions about the study drug and should start the study drug following randomization as long as conditions for administration of study drug are met. The first dose of study drug should be given at the study center following randomization. The subject, and/or the subject's parents/guardians will be trained on drug preparation and administration at the randomization visit.

The screening and randomization visits can be done on the same day if the subject is eligible by medical history, clinical exam, and has local laboratory results (either drawn 1 to 7 days prior to the consent/screening visit as part of standard of care or during the screening visit) that are

organs or tissues, and who require chronic anticoagulation for thromboprophylaxis as determined by the treating physician with guidance from major current guidelines [ACCP (American College of Chest Physicians) 2012 guideline]. To be eligible for the study, subjects under age 2 years should be expected to require anticoagulation for a minimum of 1 month; whereas subjects ≥ 2 years of age should be expected to require anticoagulation for a minimum of 6 months, although the full treatment duration of 12 months is most desirable. Eligible subjects include those who newly start anticoagulants and those who are currently on VKA or LMWH for thromboprophylaxis. The investigator is responsible for working with the treating team to determine if a subject meets the criteria for thromboprophylaxis per current ACCP guideline. Reasons for why the subject is receiving prophylaxis will be documented on the electronic case report form (eCRF).

Three age groups will be included in the study: 28 days to < 2 years, 2 years to < 12 years, and 12 years to < 18 years.

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Signed written informed consent obtained from subject's legally acceptable representative (parents or legal guardians) according to local regulations, and if the subject is mentally capable and assent is required locally, assent from the subject

2. Target Population

a) Congenital or acquired heart diseases requiring chronic anticoagulation for thromboprophylaxis (e.g., single ventricle physiology including all 3 stages of palliation, dilated cardiomyopathy, Kawasaki disease with coronary aneurysms, and pulmonary hypertension)

Note: subjects with previous history of thromboembolic events greater than 6 months prior to enrollment are eligible, provided that there is evidence (by previously obtained clinical imaging data) for thrombus stability or resolution.

b) Eligible subjects include those who newly start anticoagulants and those who are currently on VKA or LMWH or other anticoagulants for thromboprophylaxis

c) Able to tolerate enteral medication (eg, by mouth, NG tube, or G-tube)

d) Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-screened and re-consented

e) Subjects 28 days to < 3 months must be able to tolerate oral/NGT/GT feeds for at least 5 days prior to randomization

3. Age and Reproductive Status

a) Males and Females**,** 28 days to < 18 years of age, inclusive

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within

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Table 5.1-1: Screening Procedural Outline (CV185362)

Procedure	Consent/ Screening Visit Day -21 to 1	Randomization Visit Day 1	Notes
Laboratory Tests	X		CBC, ALT, AST, total and conjugated bilirubin, serum creatinine, aPTT, and INR. To avoid unnecessary blood draws, safety labs including CBC, liver and renal function tests, coagulation tests that are run 1 to 7 days prior to the consent/screening visit as part of routine clinical care may be used to satisfy the inclusion/exclusion criteria as long as the investigator believes the lab values could not have changed at enrollment Approximately 3-5 ml of blood
Pregnancy Test WOCBP only	X		Negative serum or urine pregnancy tests (minimum sensitivity 25 IU/L or equivalent units of HCG) for WOCBP within 24 hours prior to start of study drug. Note: an extension up to 72 hours is permissible in situations where pregnancy test results cannot be obtained within the standard 24 hour window
PK Sampling Apixaban subjects only		X	Day 1: 4hr (3-8hr) post dose Each sample will be approximately 1.4 mls of blood for children < 1 year of age and approximately 2 ml of blood for children ≥ 1 year of age and will be for both PK and anti-Xa activity assay PK collection with dried blood spot (DBS) technique is an option for those children < 3 months at randomization. If DBS collection is chosen, a serum PK sample must also be obtained on Day 1 The Day 1 post dose 4 hr sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban
Anti-Xa activity Apixaban subjects only		X	Day 1: 4hr (3-8 hr) post dose Each sample will be approximately 1.4 mls of blood for children < 1 year of age and approximately 2 ml of blood for children ≥ 1 year of age and will be for both PK and anti-Xa activity assay For those subjects on warfarin who are randomized to apixaban and have to

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not directly attributable to the patient's underlying medical condition and (ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

Minor bleeding: is defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or CRNM bleeding.

Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

All bleeding events and their supporting documentation **MUST** be sent for adjudication.

5.3.2 Treatment Guidelines for Bleeding / Suspected Bleeding

Subjects with bleeding or suspected bleeding should undergo confirmatory laboratory or other testing as indicated clinically (e.g., Ultrasound, Computer Tomography [CT], Magnetic Resonance Imaging [MRI]. The date and time of the onset of the bleeding event will be recorded on the CRF. The following routine measures may be considered:

- Delay the next dose of study drug or discontinue study medication if indicated
- Provide fluid resuscitation and blood transfusion as indicated
- Provide fresh frozen plasma (FFP) or general hemostatic measures as indicated

Note: There is no specific reversal agent for apixaban for use in infants and children.

Table 5.3.2-1 provides recommendations for the treatment of bleeding or suspected bleeding. The specific treatment for bleeding is left to the discretion of the investigator and/or the treating physician based on the medical status of the subject and/or institutional policies.

Table 5.3.2-1: Treatment Guidelines for Bleeding / Suspected Bleeding

Minor Bleeding	Apixaban may or may not be held based on an individualized benefit-risk assessment
Clinically Significant Bleeding / Clinically Relevant Non-Major Bleeding	Apixaban should be held if subject meets criteria outlined in section 3.5. Hold apixaban for clinically significant bleeding. Identify the source and institute local measures to stop the bleeding. • Perform laboratory test monitoring (e.g., hemoglobin, INR, aPTT, platelet count, anti-FXa activity). • Apixaban may be best monitored using an anti-FXa assay rather than the more standard coagulation tests (e.g., INR, aPTT) which are less sensitive to apixaban. • If bleeding occurs within 6 hours after apixaban administration consider administration of activated charcoal oral solution to reduce apixaban plasma exposure. • Consider appropriate symptomatic treatment (e.g., mechanical compression, surgical intervention, fluid replacement and hemodynamic support, blood product or component transfusion) • For bleeding that does not respond to local measures, consider administration of FFP as a supportive measure, recognizing that FFP does not reverse the anticoagulant effects of apixaban

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outlines the blood sampling schedule, including total amounts of blood drawn. A local laboratory should perform the laboratory tests and will provide reference ranges for these tests. The following laboratory tests are required for this study, and should be analyzed by the local laboratory: CBC, ALT, AST, and total and conjugated bilirubin, serum creatinine (estimated GFR), aPTT, INR (coagulation tests and serum creatinine at screen only), and serum or urine pregnancy test when applicable. Special kits will be provided for the PK, anti-Xa activity, [redacted] and chromogenic Factor X samples. There will be detailed instructions in a laboratory manual for specimen collection, processing, storage, and shipment. INR levels for subjects receiving VKA will either be done using the local laboratories or collected on a home monitoring device between visits and recorded in the patient's diary. Anti-Xa levels for subjects receiving LMWH will be done using the local laboratories.

5.3.4 Pregnancy Tests

For WOCBP, a serum or urine pregnancy test should have a minimum sensitivity of 25 IU/L or equivalent units of βHCG. All on-study pregnancy testing should follow the schedule detailed in Table 5.1-1.

5.3.5 Creatinine Clearance

Based on the results of the enrollment visit clinical laboratory tests, eGFR will be estimated based on the Schwartz formula (See Table 5.1-1 for timing of assessments and Appendix 5 for eGFR assessment).

Inadequate Renal Function is defined as < 30% of normal for age and size as determined by the Schwartz formula[37] [eGFR (ml/min/1.73m2) = 0.413 x (height (cm) / serum creatinine (mg/dl). If serum creatinine concentration is measured in SI units (umoles/L), divide this number by the conversion factor of 88.4 to get the SI units (mg/dl) before inserting into the Schwartz formula to calculate eGFR]. Subjects are required to have an eGFR > 30% of normal for age, gender, and height to be enrolled in the study (Appendix 5).

5.3.6 Physical Examination

A full physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, musculoskeletal, vital signs (heart rate, respiratory rate, blood pressure and temperature), height and weight.

A targeted physical examination should include any organ systems pertinent to the subject's signs, symptoms, or AES, such as assessment of signs of thromboembolism or bleeding.

Only Investigators licensed to conduct physical examinations and who are listed on the Delegation of Authority Form are approved to perform physical examinations.

5.3.7 Imaging Assessment for the Study

[redacted]

Table 5.5-1: Sampling Schedule for PK, PD [redacted] for children (1 to < 18 years of age)

Procedure	Subjects	Screening Day -21 to Day 1	Day 1[a, b]	Week 2[b] ± 3 days	Month 3[b] ± 2 weeks	Month 6[b,c] ± 2 weeks	Whole Blood Volume
Serial PK and Anti-FXa activity[c]	Subjects taking Apixaban		4 hr (3-8 hr)	Predose	2 ± 1 hr Post dose	Predose	2 ml sample for PK and anti-FXa combined
Chromogenic FX[c]	Subjects taking Apixaban		Prior to first dose[d] and 4 hr (3-8 hr)[a]		2 ± 1 hr Post dose	Predose	1.4 mL / sample
[redacted]							

[a] The Day 1 post dose 4 hr (3-8 hr) sample should be taken 3-8 hr after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr (3-8 hr) sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban.

[b] For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic Fx [redacted] samples should be drawn before the transfusion or surgery or at least a week after surgery

[c] For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation.

[d] Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1).

[redacted]

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Table 5.5-2: Sampling Schedule for PK and PD for children 3 months to < 1 years of age

Procedure	Subjects	Screening Day -21 to Day 1	Day 1[a,b]	Week 2[b] ± 3 days	Month 3[b] ± 2 weeks	Month 6[b,c] ± 2 weeks	Whole Blood Volume
Serial PK and Anti-FXa activity[c]	Subjects taking Apixaban		4 hr (3-8 hr)	Predose	2 ± 1 hr Post dose	Predose	1.4 mL sample for PK and anti-FXa combined
Chromogenic FX[c]	Subjects taking Apixaban		Prior to first dose[d] and 4 hr (3-8 hr)[a]		2 ± 1 hr Post dose	Predose	1.4 mL / sample

[a] The Day 1 post dose 4 hr sample should be taken 3-8 hr after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr (3-8 hr) sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban

[b] For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic Fx [redacted] samples should be drawn before the transfusion or surgery or at least a week after surgery

[c] For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation.

[d] Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1).

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Table 5.5-3: Sampling Schedule for PK and PD using serum samples for children 28 days to < 3 months of age

Procedure	Subjects	Day 1[a, b]	Week 2[b] ± 3 days	Month 3[b] ± 2 weeks	Whole Blood Volume
Serial PK	Subjects taking Apixaban	4 hr (3-8 hr)	Predose	2 ± 1 hr Post dose	1.4 ml sample for PK and anti-FXa combined
Anti-FXa activity	Subjects taking Apixaban			2 ± 1 hr Post dose	
Chromogenic FX	Subjects taking Apixaban	Prior to first dose[c]		2 ± 1 hr Post dose	1.4 mL / sample

a The Day 1 post dose 4 hr (3-8 hr) sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr (3-8 hr) sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban.

b For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic FX [redacted] samples should be drawn before the transfusion or surgery or at least a week after surgery

c Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1).

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Table 5.5-4: Sampling Schedule for PK and PD using dried blood spot (DBS) sampling for children 28 days to < 3 months of age [d]

Procedure	Subjects	Day 1[a, b,c,d]	Week 2[b] ± 3 days	Month 3[b] ± 2 weeks	Whole Blood Volume
Serial PK [e]	Subjects taking Apixaban	4 hr (3-8 hr)	Predose	2 ± 1 hr Post dose	1.4 ml serum sample for PK at Day 1 only PK and anti-FXa sample combined 60-80 uL for PK DBS samples at Day 1, Week 2, and Month 3
Anti-FXa activity	Subjects taking Apixaban			2 ± 1 hr Post dose	
Chromogenic FX	Subjects taking Apixaban	Prior to first dose[c]		2 ± 1 hr Post dose	1.4 mL / sample

a The Day 1 post dose 4 hr (3-8 hr) sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr (3-8 hr) sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban.

b For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic FX [redacted] samples should be drawn before the transfusion or surgery or at least a week after surgery

c Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1).

d A single PK serum sample will be collected at the Day 1 visit only for subjects using DBS collection

e Dried blood spot (DBS) may be used as an alternative collection method for PK in subjects under the age of 3 months at the time of randomization. If an investigator opts to use DBS, it must be used for all PK collection points.

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5.7 Outcomes Research Assessments

Quality of Life (QOL) instruments will be given to all English speaking subjects who have been previously taking an anticoagulant at the Day 1 visit. These include patient/proxy reported outcome or quality of life (e.g, pediatric quality of life inventory [PedsQL]) generic core and cardiac modules, and Kids Informed Decrease Complications Learning on Thrombosis [KIDCLOT©]). Subjects who are newly prescribed an anticoagulant at study entry will be given the PedsQL at the Day 1 visit, but because some exposure to anticoagulation therapy is necessary to complete the KIDCLOT, they will be given the KIDCLOT at the Week 2 visit. The QOL instruments need to be completed at the time of the visit.

Additionally, the QOL instruments will be administered at the Month 6 visit, the end of study treatment (for subjects who discontinue study drug early) or Month 12 visit.

5.8 Other Assessments

Not applicable.

6 ADVERSE EVENTS

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

The causal relationship to study drug is determined by a physician and should be used to assess all AE. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

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The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

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

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE
- Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting of pregnancies)
- Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details)

NOTE:

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

- a visit to the emergency room or other hospital department lasting < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)

- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, or other administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) and the local product label for apixaban represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. For active comparators VKA and LMWH, the local product label (e.g., USPI, SmPC, etc.) will be used as Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs that occur during the screening period and within 30 days of discontinuation of dosing must be collected.

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

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission,

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paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

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

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

6.3 Laboratory Test Result Abnormalities

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

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least

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5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose, if excessive and medically important, must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

The following guidelines are intended to identify and manage subjects with liver function abnormalities. Specific laboratory test criteria and instructions for further follow up are provided.

If at any time during the treatment period a subject's liver function test (LFT) results show:

- An isolated elevation of either ALT/AST ≥ 5 x ULN AND/OR a direct (conjugated) bilirubin > 2 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, CK as soon as possible (i.e. within 3 days)
- If the repeat tests indicate:
  - ALT/AST < 5 x ULN and conjugated bilirubin ≤ 2 x ULN, study medication may continue
  - ALT/AST ≥ 5 x ULN AND/OR the conjugated bilirubin is > 2 x ULN, the study medication must be interrupted

The study medication must be interrupted if:

- Clinical jaundice is present in a subject at any time unless there is an alternative causative factor such as Gilbert or Dubin-Johnson syndrome

OR

- If ALT/AST ≥ 5 x ULN on any two consecutive occasions

OR

- Conjugated bilirubin > 2 x ULN on any two consecutive occasions

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Due to anticipated low rates of thromboembolic[6] and bleeding[5,6] events in the study population and other numerous barriers,[38] a Phase 3 trial requiring an excessively large sample size is impracticable. However, there remains a need to understand the safety and PK/PD profile of apixaban in children with heart disease and gather preliminary data on efficacy that could be used to develop future studies. Therefore, the study is designed to obtain apixaban PK, PD, safety information, and exploratory efficacy data, and is a descriptive study for which the safety, PK/PD, and efficacy variables will be summarized. The study will still include a randomized comparison group with standard anticoagulants as a frame of reference regarding frequencies of bleeding and thromboembolic events in the pediatric setting. This approach has been recommended by the Subcommittee on Pediatric and Neonatal Hemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis (ISTH).[39]

With a treatment period up to 12 months, the sample size of approximately 200 subjects (approximately 133 in the apixaban group and approximately 67 in the SOC group) is a feasible sample size that will provide a robust PK/PD database, and reasonable safety data along with limited efficacy data in pediatric subjects with heart disease who need chronic thromboprophylaxis. More specifically, approximately 533 blood samples will be obtained during the study to characterize apixaban PK and PD in approximately 133 apixaban treated subjects aged 28 days to < 18 years. The data collected in the current study will be combined with available data from two other pediatric PK studies for population PK/PD analyses, providing the ability to fully capture the pharmacokinetic disposition in this special patient population. In addition, these analysis will provide robust data to inform apixaban dosing in the pediatric cardiac population across a broad age spectrum. The observed AE, bleeding events, QOL and efficacy data from this study will provide insight into the expected event rates for the pediatric population treated with apixaban or SOC to inform benefit-risk.

The following examples of potential results, with anticipated precision around the estimate, may provide an understanding of the data that the study will generate, and may offer insight into how the trial data may be interpreted.

Possible Safety Outcome

The primary safety endpoint (a composite of adjudicated major or clinically relevant non-major bleeding) event rate is not well characterized in children. Based on two randomized studies in pediatric patients with congenital heart disease,[6,5] one randomized study in pediatric patients with VTE events[40], and adult data in the stroke prevention trial ARISTOTLE[17], event rates of 2 to 12% may be expected. Based on this event rate range, the following may be a safety outcome of this trial:

Table 8.1-3: Difference in Event Rates and 95% Confidence Intervals between Comparator Group and Apixaban Group

Event Rate for Comparator (N=67)	Event Rate for Apixaban (N=133)	Difference of Event Rates (Comparator-Apixaban)	95% CI (%) of Difference of Rates
3%	2.3%	0.7%	-4.0 to 8.1
	6%	-3%	-8.9 to 4.8
	9.8%	-6.8%	-13.4 to 1.5
10.5%	2.3%	8.2%	1.5 to 17.9
	6%	4.5%	-3 to 14.5
	9.8%	0.7%	-7.5 to 11.1
	15%	-4.5%	-13.4 to 6.3
	22.6%	-12.1%	-21.6 to -0.7

CI - confidence interval

Potential Power to Detect Possible Differences between Apixaban and Comparator in Safety Endpoints

As discussed above, this study is intended to provide safety and PK data for at least 133 patients exposed to apixaban, and is not expected to be fully powered for either efficacy or safety due to the low incidence of thromboembolic and bleeding events in children. For completeness, however, a range of power for the primary safety endpoint is provided in Table 8.1-4 and Table 8.1-5. This estimation is based on a sample size of approximately 200 subjects and an event rate range of 2-12%, using Fisher's exact test and a 2-sided 0.05 significance level. Both scenarios of better safety and worse safety of apixaban relative to comparator are displayed.

Table 8.1-4: Possible Power to Detect a Significant Difference between Comparator Group and Apixaban Group for the Primary Safety Endpoint (Assuming Apixaban is Better)

Comparator			Apixaban			Power to Detect a Significant Difference
Sample Size	Event Rate	Expected Number of Events	Sample Size	Event Rate	Expected Number of Events	
67	11.9%	8	133	2.3%	3	75%
	13.4%	9		2.3%	3	83%
	11.9%	8		3.8%	5	65%
	16.4%	11		3.8%	5	82%
	11.9%	8		6%	8	27%
	23.9%	16		8.3%	11	81%

Note: The primary safety endpoint will be a composite of adjudicated major or clinically relevant non-major bleeding. Power is calculated using Fisher's exact test and a two-sided alpha=0.05.

Table 8.1-5: Possible Power to Detect a Significant Difference between Comparator Group and Apixaban Group for the Primary Safety Endpoint (Assuming Apixaban is Worse)

Comparator			Apixaban			Power to Detect a Significant Difference
Sample Size	Event Rate	Expected Number of Events	Sample Size	Event Rate	Expected Number of Events	
67	3%	2	133	11.3%	15	47%
	3%	2		15.8%	21	84%
	4.5%	3		11.3%	15	28%
	4.5%	3		18.8%	25	82%
	6%	4		11.3%	15	35%
	6%	4		21.1%	28	81%
	9%	6		15.8%	21	30%
	9%	6		25.5%	34	80%

Note: The primary safety endpoint will be a composite of adjudicated major or clinically relevant non-major bleeding. Power is calculated using Fisher's exact test and a two-sided alpha=0.05.

8.2 Populations for Analyses

- The safety population for safety endpoints includes all subjects who receive at least one dose of study medication
- The population for efficacy analysis includes all randomized subjects
- The analysis population for PK assessments will include subjects who have received at least one dose of apixaban and have a PK sample collected
- The analysis population for PD assessments will include subjects who have received at least one dose of apixaban and have a PD sample collected

Pre-specified, descriptive subgroup analysis will be performed for subjects with or without a previous history of thromboembolic events, for subjects with or without aspirin use, and other important subgroups, if applicable. Details will be provided in the Statistical Analysis Plan (SAP).

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Primary efficacy endpoint: This is a safety and PK study, and there is no primary efficacy endpoint in this study.

Primary safety endpoint: A composite of adjudicated major or CRNM bleeding events per the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria.

Note: bleeding occurring within 24 hours after cardiac catheterization and bleeding occurring within 48 hours after surgery will be analyzed separately. Details will be described in the Statistical Analysis Plan (SAP).

Bleeding definitions are described as follows:

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 (i.e. 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.

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 subject's underlying medical condition; and/or ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

Both major and CRNM bleeding events will be adjudicated by a blinded, independent EAC.

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8.3.2 Secondary Endpoint(s)

Pharmacokinetics:

Apixaban PK will be characterized using a population PK approach. Nonlinear mixed effects modeling will be used to estimate population and individual PK parameters (e.g., CL/F, Vc/F, Ka), and to explore relationships between these parameters and subject demographics (e.g., age, body weight, gender) as well as estimate Cmax, Cmin, and AUC (TAU) in each subject. Data from this study may be combined with data from prior apixaban pediatric trials.

Chromogenic FX assay (apparent FX level) will be measured to assess apixaban PD. Anti-FXa activity will also be assessed.

Apixaban exposure-response (E-R) relationships may also be explored.

Efficacy:

- Any thromboembolic events (intra-cardiac, shunt, inside Fontan pathway, PE, stroke, other arterial or venous thromboembolic events, etc.) detected by imaging or clinical diagnosis, and thromboembolic event-related death

  Note: thrombosis occurring within 24 hours after cardiac catheterization and thrombosis occurring within 48 hours after surgery will be analyzed separately. Details will be described in the SAP.

- Death and thromboembolic events will be adjudicated by a blinded, independent EAC
- Patient/proxy reported outcome or quality of life (e.g., pediatric quality of life inventory (PedsQL) generic core and cardiac modules, and Kids Informed Decrease Complications Learning on Thrombosis [KIDCLOT©])

Safety:

- Adjudicated major bleeding
- Adjudicated CRNM bleeding
- All bleeding
- Drug discontinuation due to adverse effects, intolerability, or bleeding
- All cause death

[redacted]

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8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group (apixaban and active comparator) and for all subjects combined. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate and heart rate) and medical history.

8.4.2 Efficacy Analyses

There is no primary efficacy endpoint for this study. For the secondary and other efficacy endpoints, descriptive statistics including event rates will be provided. Difference of event rates and 95% confidence interval (CI) if applicable will also be provided, and relative risk and 95% CI for relative risk will be calculated based on the stratified Mantel-Haenszel's method if applicable. Efficacy analyses will be based on intention to treat (ITT) population.

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8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

There will be no formal interim efficacy analysis because this is not a Phase 3 trial powered for efficacy.

Interim safety analysis will be performed per the DSMB requirement. The DSMB will review safety and efficacy outcomes as defined in the DSMB charter. Detailed monitoring rules will be provided in the DSMB data monitoring plan. The DSMB may recommend termination of the study or any of the study arms for an important safety concern that is felt to outweigh potential benefits.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

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

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

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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Term	Definition
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	
CL	clearance
[redacted]	
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CPB	cardiopulmonary bypass
[redacted]	
CRF	Case Report Form, paper or electronic
[redacted]	
CVAD	central venous access device
CYP	cytochrome p-450
[redacted]	
dL	deciliter
[redacted]	
DSMB	data safety monitoring board
[redacted]	
EAC	Events adjudication committee
[redacted]	
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	
e.g.	exempli gratia (for example)
EMRs/EHRs	electronic medical/health records
E-R	exposure-response
[redacted]	
F	bioavailability

Table 1: Blood Sampling Schedule and volumes for Safety Labs, PK, PD [redacted] (for Ages 3 months to < 18 years)

Procedure	Subjects	Screening Day -21 to Day 1	Day 1[a,f]	Week 2[f] ±3 days	Month 3[f] ± 2 weeks	Month 6[b,f] ± 2 weeks	Month 12 ± 2 weeks	Comments
Total Blood Taken	Subjects taking Apixaban	5.7 - 7.7 ml	4.2- 4.8 - ml	7.1 - 9.7 ml	5.8 -8.4 ml	8.5-11.1- - ml	3 - 5 ml	Total = 34.3 – 46.7 ml (during the whole study) [e]
	Subjects taking VKA or LMWH	5.7 - 7.7 ml	0 ml	5.7 - 7.7	3 - 5 ml	5.7 - 7.7 ml	3 - 5 ml	Total = 23.1 - 33.1 ml (during the whole study) [e]

a The Day 1 post dose 4 hr sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr sample should be postponed and only be done 3-8 hrs after the subject has taken their first dose of apixaban

b For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation + 2 weeks.

c INR, aPTT and Serum creatinine will be measured at screening only.

d Pregnancy tests will be measured in women of child bearing potential only.

[redacted]

f For subjects undergoing surgery and possibly getting a transfusion, the PK, chromogenic Fx [redacted] sample should be drawn either before the transfusion or surgery or at least a week after surgery

[redacted]

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Table 3: Sampling Schedule for Safety labs, PK (using dried blood samples), and PD (ages 28 days to < 3 months of age) h

Procedure	Subjects	Screening	Day 1[a, b]	Week 2[b] ±3 days	Month 3[b] ± 2 weeks	Month 6 [b]	Month 12	Whole Blood Volume
Safety Labs:CBC, AST/ALT, T/D bilirubin INR[e], aPTT[e], Serum creatinine[e] Pregnancy [f]	All subjects	X		X	X	X	X	~3-5 ml
Serial PK[c,g,h]	Subjects taking Apixaban		4 hr[g,h] (3-8 hr)	Predose[h]	2 ± 1 hr Post dose[c,h]			1.4 ml for PK and Chromogenic Anti-Fx sample at Day 1 2 ml combined sample for anti-FX and chromogenic dose FX at Month 3 60-80 uL for PK DBS samples at Day 1, Week 2, and Month 3
Anti-FX a activity[c]	Subjects taking Apixaban				2 ± 1 hr Post			
Chromogenic FX[c]	Subjects taking Apixaban		Prior to first dose[d]		2 ± 1 hr Post dose			
Total Blood Taken		3-5 ml	2. 88 ml	3.08-5.08 ml	5.08-7.08 ml	3-5 ml	3-5 ml	Total = 20.4 – 30.4 ml (during the whole study)

a The Day 1 post dose 4 hr sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr sample should be postponed and only be done 3-8 hrs after the subject has taken their first dose of apixaban.

b For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic Fx should be drawn before the transfusion or surgery or at least a week after surgery

c For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation.

d Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1)

e INR, aPTT and Serum creatinine will be measured at screening only.

f Pregnancy tests will be measured in women of child bearing potential only

g If DBS PK sampling is used, a single PK serum sample will be collected at the Day 1 visit

h Dried blood spot (DBS) may be used as an alternative collection method for PK in subjects under the age of 3 months at randomization. If an investigator opts to use DBS, it must be used for all PK collection points

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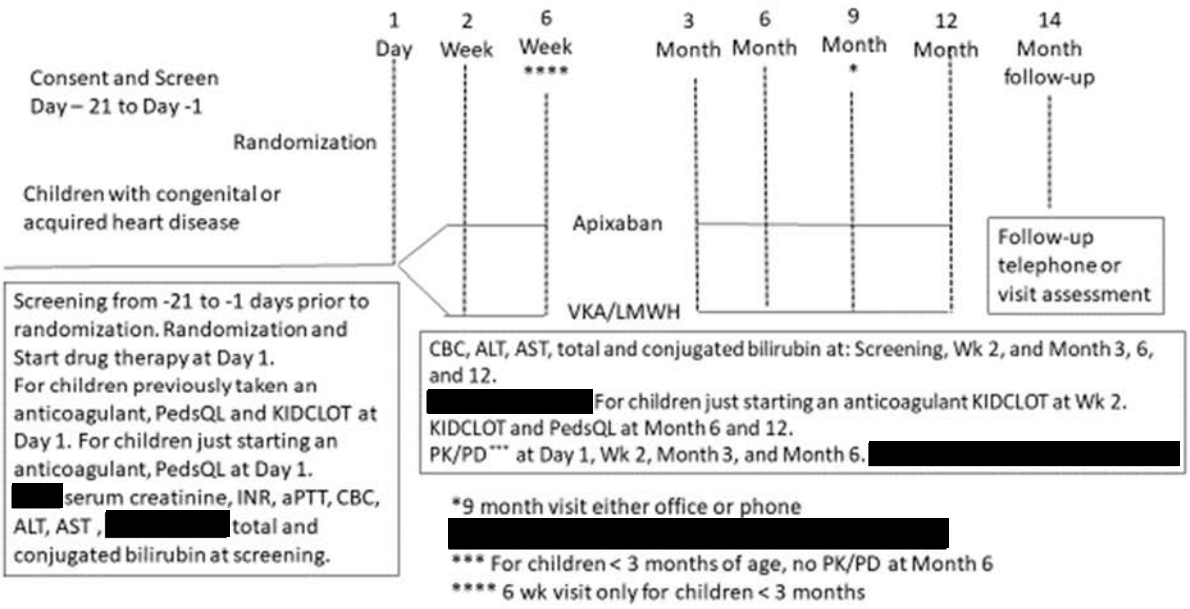
Study Design



Study Population:

Subjects eligible for the study include both males and females, 28 days to < 18 years of age, with congenital or acquired heart disease who are at risk for thrombus formation that can result in vascular, intracardiac or coronary artery thrombosis, or embolization to other organs or tissue, and who require chronic anticoagulation for thromboprophylaxis as determined by the treating physician with guidance from major current guidelines (ACCP 2012 guideline). To be eligible for the study, subjects under age 2 years should be expected to require anticoagulation for a minimum of 1 month; whereas subjects ≥ 2 years of age should be expected to require anticoagulation for a minimum of 6 months, although the full treatment duration of 12 months is most desirable. Subjects who are expected to be chronically anticoagulated (> 1 year), should have a study treatment duration of 12 months. Eligible subjects include those who newly start anticoagulants and those who are currently on VKA or LMWH for thromboprophylaxis. The investigator is responsible for working with the treatment team to determine if a subject meets the criteria for thromboprophylaxis per the current ACCP guideline. The reasons the subject is receiving prophylaxis will be documented on the eCRF.

Three age groups will be included in the study: 28 days to < 2 years, 2 years to < 12 years, and 12 years to < 18 years. Every effort will be made to ensure appropriate representation for each of the age groups. The neonate cohort will be removed from the study population [redacted] upon approval of this revised protocol.

[redacted] Recruitment started in January 2017 for children of ages ≥ 2 to < 18 years and was extended to children ages 3 months to < 2 years in December 2017. Recruitment opened to children 28 days to < 3 months old in February 2020.

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Apixaban PK has been well characterized in adults. It has an oral bioavailability of approximately 50%, a half-life of approximately 12 hours and is eliminated by multiple pathways including metabolism, renal excretion and excretion into the gastrointestinal tract. Renal clearance accounts for approximately 27% of apixaban total clearance. Modest increases in apixaban exposure (38-44%) have been observed in subjects with severe renal impairment (creatinine clearance 15 - 30 mL/min) and subjects with end stage renal disease on chronic hemodialysis. Moderate hepatic impairment (Child-Pugh Class B) did not impact apixaban exposure. Due to its multiple elimination pathways and lack of inhibition of major metabolic enzymes or drug transporters, apixaban is not expected to have significant drug-drug interactions. However, apixaban is a substrate for CYP3A4 enzyme and the P-gp transporter, therefore, its absorption and elimination may be affected by CYP3A4 and /or P-gp modulators. Strong dual inhibitors of CYP3A4 and P-gp, such as ketoconazole, can increase apixaban exposure by approximately 2-fold.

Consistent with its mechanism of action, apixaban can increase clotting time measures such as activated partial thromboplastin time (aPTT), International Normalized Ratio (INR) as well as affect other coagulation assessments (anti-Xa activity, thrombin generation, etc.). However, apixaban has been shown to have minimal impact on the aPTT, or INR at therapeutic concentrations. Measurement of anti-FXa activity, using a one-step chromogenic assay is appropriately sensitive enough to detect its presence[26].

To support the apixaban pediatric development plan, additional clinical pharmacology studies have been completed and are described below.

The palatability and relative bioavailability of apixaban oral solution have been assessed in healthy adult subjects. Based on these studies the apixaban oral solution is expected to have acceptable palatability for the pediatric population and has comparable bioavailability to the apixaban tablet formulation. In addition, administration of the oral solution or a crushed tablet via a NGT flushed with 60 mL D5W achieves similar exposure to oral administration of the apixaban solution. Apixaban relative bioavailability appears to be 8% to 20% lower following administration of the oral solution via NGT using infant formula or an enteral meal, such as Boost Plus, as a flush medium.

The palatability and relative bioavailability of apixaban 0.1 mg capsules dispersed in water relative to the 0.5 mg tablets dispersed in water have been assessed in healthy adult subjects. Based on this study, both of these pediatric formulations are expected to have acceptable palatability. The results of this study demonstrated comparable AUC was achieved with both formulations, but the Cmax was ~30% higher with the 0.1 mg capsule formulation compared to the 0.5 mg tablet formulation.

An in vitro comparison study was performed in pediatric and adult plasma samples spiked with apixaban to compare and characterize the PD activity of apixaban in pediatric and adult plasma samples. This study demonstrated that, relative to adults, Factor X levels are lower in plasma samples from children 6 months of age and younger as well as in umbilical cord blood; this observation is consistent with literature reports of developmental hemostasis. Despite the lower

within the appropriate inclusive parameters. The pregnancy test must be performed within 24 hours prior to the start of study drug. An extension up to 72 hours is permissible in situations where pregnancy test results cannot be obtained within the standard 24 hour window.

Blood samples will be taken for PK, anti-FXa, and Chromogenic FX assessment at randomization visit (see Table 5.5-1, Table 5.5-2, Table 5.5-3, and Table 5.5-4 for details). [redacted] Dried Blood Spot Sampling (DBS) will be an option for PK sample collection in subjects < 3 months at the time of randomization.

[redacted]

Quality of Life (QOL) instruments will be given to all English speaking subjects who have been previously taking an anticoagulant at the Day 1 visit. These include patient/proxy reported outcome or quality of life (e.g, pediatric quality of life inventory [PedsQL]) generic core and cardiac modules, and Kids Informed Decrease Complications Learning on Thrombosis [KIDCLOT©]). Subjects who are newly prescribed an anticoagulant at study entry will be given the PedsQL at the Day 1 visit, but because some exposure to anticoagulation therapy is necessary to complete the KIDCLOT©, they will be given the KIDCLOT© at the Week 2 visit. The QOL needs to be completed at the time of the visit (see Table below).

QOL Assessment Schedules		
	Subjects new to anticoagulants	**Subjects previously on anticoagulants**
PedsQL	Day 1, Months 6 and 12	Day 1, Months 6 and 12
KidsClot	Week 2, Months 6 and 12	Day 1, Months 6 and 12

During the Treatment Period, in-person study visits will occur at 2 weeks ± 3 days, 3 months ± 2 weeks, 6 months ± 2 weeks, and 12 months ± 2 weeks. Study visits should be scheduled from a starting point of 'Day 1' in order to ensure that a 12 month treatment duration is achieved. Subjects who are < 2 years of age will have a mandatory in-person visit at 9 months ± 2 weeks to include weight measurement, dose adjustment (if necessary) reporting adverse events, and assessing medication adherence. Subjects who are ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. Subjects aged 28 days to < 3 months at the time of randomization will have an office visit at 6 weeks ± 3 days for assessment of body weight in order to adjust the dose of study medication (if necessary).The phone visit will monitor

24 hours prior to the start of study drug. An extension up to 72 hours is permissible in situations where pregnancy test results cannot be obtained within the standard 24 hour window

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with apixaban plus 5 half-lives of the drug (2 days) plus 30 days (duration of ovulatory cycle) for a total of 32 days post-treatment completion. For VKA and LMWH, please follow the local product label for instructions on contraception.

e) Not applicable as per amendment 03

f) Not applicable as per amendment 03

Investigators shall counsel all subjects who are 12 years of age or older, as well as any female subjects who are less than 12 years of age but who meet the definition of WOCBP and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use one highly effective OR one less effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and WOCBP, who are partners of male subjects, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomized partner with documented azoospermia 90 days after procedure
   a. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success
6. Intrauterine hormone-releasing system (IUS)
7. Complete abstinence
   a. Complete abstinence is defined as the complete avoidance of heterosexual intercourse

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Table 5.1-1: Screening Procedural Outline (CV185362)

Procedure	Consent/ Screening Visit Day -21 to 1	Randomization Visit Day 1	Notes
			wait for their INRs to be within range before starting apixaban, the Day 1 post dose 4 hr sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban For those children < 3 months of age at randomization, blood samples will not be taken at Day 1.
Chromogenic FX assay Apixaban subjects only		X	Day 1 Prior to 1st dose, 4 hr (3- 8 hr) post dose Each sample will be approximately 1.4 ml of blood For those subjects on warfarin who are randomized to apixaban and have to wait for their INRs to be within range before starting apixaban, the Day 1 post dose 4 hr (3-8 hr) sample should be postponed and only be done 3-8 hr after the subject has taken their first dose of apixaban
[redacted]			
Efficacy Assessments			
QOL assessment		X	PedsQL and KIDCLOT QOL instruments to be administered to English speaking subjects who have been previously taking an anticoagulant. Subjects newly taking anticoagulants will be given the PedsQL only at this visit. The QOL instruments needs to be completed at the time of the visit
Study Drug Supplies			
Enroll via IWRS	X		
Randomize via IWRS		X	Subjects can be enrolled and randomized during the same visit.
Dispense Study Drug		X	Apixaban, warfarin and enoxaparin will be supplied by BMS or warfarin and

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Table 5.3.2-1:	Treatment Guidelines for Bleeding / Suspected Bleeding
Life Threatening Bleeding / Major Bleeding	Apixaban should be held for all life threatening bleeding. • Administration of recombinant Factor VIIa may be considered, however, there is no experience with this agent in apixaban-treated patients. Its effectiveness for counteracting the effects of apixaban is not known. • Activated prothrombin complex concentrate (aPCC) or prothrombin complex concentrate (PCC, also referred to as factor IX concentrate) are other procoagulants that may be considered, but considering the variety of formulations available and the complexity of dosing, the decision to employ aPCC or PCC should be made by an experienced clinician with careful evaluation of the risks and benefits. • If bleeding occurs within 6 hours after apixaban administration activated charcoal oral solution administration may be considered in order to reduce apixaban plasma exposure.

[redacted]

Please follow the product label or institutional protocol for the treatment of bleeding associated with VKA or LMWH.

5.3.3 Laboratory Assessments

Blood samples will be obtained on selected visits of clinical laboratory evaluations as outlined in Section 5.1 (Table 5.1-1 and Table 5.1-2 - Flow chart/ Time and Events Schedule). Appendix 1

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[redacted]

Routine mandatory images for thromboembolic events are not required for the study. However, any clinical, radiologic and catheter evaluations prompted by clinical suspicion of any thromboembolic events, bleeding or death can be performed at the discretion of the site principal investigator and/or treating clinician; information from these visits and findings will be captured for study analysis.

5.4 Efficacy Assessments

This is a safety and PK study, and there is no primary efficacy assessment in this study. The secondary assessments include any thromboembolic events (intra-cardiac, shunt, inside Fontan pathway, PE, stroke, other venous or arterial thromboembolic events) detected by imaging or clinical diagnosis, and thromboembolic event-related death. Thromboembolic event-related death and thromboembolic events will be adjudicated by a blinded, independent EAC.

5.5 Pharmacokinetic and Pharmacodynamic Assessments

Samples for PK and PD (Chromogenic FX assay) will be taken in subjects receiving apixaban only. Chromogenic FX assay which measures (apparent) FX level will be used to assess endogenous FX level at baseline and inhibition of FXa by apixaban. In addition, anti-FXa activity, which uses exogenous FXa and apixaban calibrators will be measured in subjects receiving apixaban to assess their plasma apixaban levels. PK samples may be analyzed for the concentration of apixaban in a timely manner during the study, if needed. There will be special kits and detailed instructions in a laboratory manual provided for specimen collection, processing, storage, and shipment. For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic Fx samples should be drawn before the transfusion or surgery or at least a week after surgery.

Table 5.5-1, Table 5.5-2, Table 5.5-3, and Table 5.5-4 summarizes the sampling collection schedule for children ≥ 1 to < 18 years of age, infants 3 months to < 1 years of age, infants 28 days to < 3 months using whole blood, and infants 28 days to < 3 months using dried blood spot (DBS) respectively (for PK, PD[redacted]). (See Appendix 1 for additional information including total amount of blood drawn during the study). Attempts should be made to coordinate blood sampling with the blood draw for safety labs.

All subjects with an ALT/AST ≥ 5 x ULN or direct bilirubin > 2 x ULN will be followed weekly until ALT/AST returns to < 3 x ULN or to baseline, and the conjugated bilirubin returns to ≤ 1.5 x ULN or to baseline.

If study medication is discontinued due to elevated ALT, AST, OR bilirubin, as defined above, inform the medical Monitor and perform the following:

- aPTT, fibrinogen to assess liver synthetic function
- Abdominal ultrasound, including liver and hepatobiliary system
- Hepatitis screen (anti-HAV, HBsAg, anti-HBc, anti-HBs and anti-HCV)
- Obtain relevant specialist consultation

6.7 Other Safety Considerations

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

7 DATA AND SAFETY MONITORING BOARD AND OTHER EXTERNAL COMMITTEES

7.1 Data and Safety Monitoring Board

This study will be conducted under the monitoring of an independent Data Safety Monitoring Board (DSMB), whose activities will be described in a DSMB charter. In addition, the DSMB will use their clinical and statistical judgment to recommend that the study proceed or be terminated early.

7.2 Steering Committee

An academic Steering Committee, participated in the development of the protocol, and will provide ongoing scientific and operational oversight to the study. The Steering Committee will monitor all aspects of the study, make recommendations to the sponsor and the Pediatric Heart Network (PHN) based on the DSMB recommendations, and oversee the presentation of the trial results and any publications.

7.3 Event Adjudication Committee

The EAC, as described in the EAC charter, is an independent committee constituted by experienced clinicians independent of the Investigators and the Sponsor. The responsibilities of the EAC are 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 primary analyses.

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Table 8.1-1: Number of Safety Events, Event Rate, and 95% Confidence Intervals for the Primary Safety Outcome in the Apixaban Group (N=133)

# of Events	Event Rate	95% CI (%)
2	1.5%	0.2 to 5.3
3	2.3%	0.5 to 6.4
4	3%	0.8 to 7.5
7	5.3%	2.1 to 10.5
9	6.8%	3.1 to 12.5
16	12%	7.0 to 18.8

Note: The primary safety outcome will be the incidence of adjudicated major or clinically relevant non-major bleeding. Each type of adjudicated bleeding will be summarized using counts and frequencies in each treatment arm.

Table 8.1-2: Number of Safety Events, Event Rate, and 95% Confidence Intervals for the Primary Safety Outcome in the Comparator Group (N=67)

# of Events	Event Rate	95% CI (%)
1	1.5%	0 to 8.0
2	3%	0.4 to 10.4
4	6%	1.7 to 14.6
5	7.5%	2.5 to 16.6
6	9%	3.4 to 18.5
8	11.9%	5.3 to 22.2

Note: The primary safety outcome will be the incidence of adjudicated major or clinically relevant non-major bleeding. Each type of adjudicated bleeding will be summarized using counts and frequencies in each treatment arm.

To further provide an understanding of the data that the study will generate, examples of potential differences in bleeding event rates and anticipated precision around the estimate between apixaban and comparator are shown in Table 8.1-3. Since the relative safety profile of apixaban in pediatric patients with cardiac disease is unknown, both scenarios of better safety and worse safety of apixaban relative to comparator are displayed.

8.4.3 Safety Analyses

The term "treatment period" refers to the period between the first administration of study drug and two days after the last administration of study drug. This period will be the basis for the summaries of safety.

Primary Safety Analyses

For the primary safety endpoints, descriptive statistics including event rates, difference of event rates and 95% confidence interval (CI) will be provided, and relative risk and 95% CI for relative risk will be calculated based on the stratified Mantel-Haenszel's method if applicable.

Secondary Safety Analyses

The incidence of minor bleeding events and all bleeding AEs occurring through the end of the treatment period will be summarized by treatment group. The incidence of AEs and of marked abnormalities in clinical laboratory tests will be summarized by treatment group. All AEs that are serious or that result in discontinuation of study drug will be described in depth. Changes from baseline in laboratory parameters will be summarized at each measurement time point by treatment group.

8.4.4 Pharmacokinetic Analyses

Samples collected for pharmacokinetic analysis will be analyzed by LC-MSMS to determine apixaban plasma concentration. A PPK model will be developed using plasma concentration versus time data. Model-derived population and individual PK parameters (e.g., CL/F, Vc/F, KA) will be used to estimate Cmax, Cmin, and AUC(TAU) in each subject. Details of the analyses will be described in a separate population PK/PD modeling analysis plan document and results will be presented in a separate population PK/PD report. Summary Statistics will be provided by age- and weight-group as appropriate. Listings of individual observed PK will be provided by visit, weight- and age-group as appropriate.

[redacted]

8.4.6 Outcomes Research Analyses

The analysis method for QOL will be provided in the statistical analysis plan. It is anticipated that apixaban may have more impact on KIDCLOT© that measures the treatment effect of an anticoagulant, and may have less impact on PedsQL generic core and cardiac modules that measures disease burden.

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Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source document:

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

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

Term	Definition
[redacted]	
FDA	Food and Drug Administration
[redacted]	
FXa	factor 10a
g	gram
[redacted]	
GCP	Good Clinical Practice
[redacted]	
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
[redacted]	
HCV	hepatitis C virus
[redacted]	
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	
HR	heart rate
[redacted]	
IB	Investigator Brochure
[redacted]	
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IWRS	Interactive web response system
kA	Acid dissociation constant
[redacted]	
kg	kilogram

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Table 2: Blood Sampling Schedule and volumes for Safety Labs, PK (using blood samples), and PD (ages 28 days to < 3 months of age)

Procedure	Subjects	Screening	Day 1[a, b]	Week 2[b] ±3 days	Month 3[b] ± 2 weeks	Month 6[b]	Month 12	Whole Blood Volume
Safety Labs:CBC, AST/ALT, T/D bilirubin INR[e], aPTT[e], Serum creatinine[e]	All subjects	X		X	X	X	X	~3-5 ml / sample
Serial PK [c]	Subjects taking Apixaban		4 hr (3-8 hr)	Predose'	2 ± 1 hr Post dose			1.4 ml sample for PK and anti-FXa combined
Anti-FX a activity [c]	Subjects taking Apixaban				2 ± 1 hr Post dose			
Chromogenic FX [c]	Subjects taking Apixaban		Prior to first dose[d]		2 ± 1 hr Post dose			1.4 mL / sample
Total Blood Taken		3-5 ml	2.8 - ml	4.4-6.4 ml	5.8-7.8 ml	3-5 ml	3-5 ml	Total = 22 - 32 ml (during the whole study)

a The Day 1 post dose 4 hr sample should be taken 3-8 hrs after the first apixaban dose. For those subjects on VKA prior to study entry who are randomized to apixaban, and have to wait for their INRs to be below 2 before starting apixaban, the Day 1 post dose 4 hr sample should be postponed and only be done 3-8 hrs after the subject has taken their first dose of apixaban.

b For subjects undergoing surgery and possibly getting a transfusion, the PK/PD and chromogenic Fx should be drawn before the transfusion or surgery or at least a week after surgery

c For subjects who discontinue before the month 6 visit, blood samples will be taken at the end of the treatment discontinuation.

d Blood samples can be taken any time prior to the first dose of study drug at randomization (Day1)

e INR, aPTT and Serum creatinine will be measured at screening only.

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Pediatric Blood Draw Guidance

NIH Clinical Center guidelines recommends no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

The NIH Clinical Center guidelines can be found at https://irb.research.chop.edu/sites/default/files/documents/g_**nih_blooddraws**.pdf

A review by Stephen Howie: Blood sample volumes in child health research: review of safe limits can be found at

http://www.who.int/bulletin/volumes/89/1/BLT-10-080010-table-T2.html

A summary table from the review paper is provided below:

Table 2 Policies and recommendations on safe blood sample volume limits for paedriatric clinical research as identified through a review of the literature

Table 2. **Policies and recommendations on safe blood sample volume limits for paediatric clinical research as identified through a review of the literature**

Institution/Body	Maximum volume allowed for a single draw		Maximum cumulative draw volume allowed
	% of TBV	ml/kg	
Toronto Hospital for Sick Children Research Ethics Board[29]	5	*3.75–4.0*[a]	5% of TBV within 3 months
USC/LA Children's Hospital[22]	*2.5–2.7 (within 24 hour)*[a]	2	4 ml/kg within 30 days
Wayne State University[23]	1	0.8	10% of TBV or 8 ml/kg within 8 weeks
Partners Human Research Committee[24]	*3.6–3.9*[a]	<3	<3 ml/kg within 8 weeks
University of California Davis[25]	*2.5* *Note: Minimum blood Hb required at time of blood draw, 7 g/dl (9–10 g/dl if cardiorespiratory compromise present)*	*2*[a]	5% of TBV within 30 days
Duke University[26]	For expedited IRB approval		3 ml/kg or 50 ml total (whichever is less) over 8 weeks
	2.5[a] (for review by convened IRB; *note: special precautions and justification required for more than this limit*)	2, up to 200 ml total	7 ml/kg over 8 weeks (up to 5 draws of 7 ml/kg per year)
KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya[b]	*1.9–2.3*[a] (2005 guideline for *total* volume drawn)	1.7–2.4	Not stated
	1.3[a] (2008 guideline for volume drawn for *research* purposes in addition to volume needed for routine care)	1	5 ml/kg within 8 weeks
US Dept of Health and Human Services, Office for Human Research Protections[17]	*3.8*[a]	3, up to 50 ml total	3 ml/kg, up to 50 ml total within 8 weeks
Kauffman 2000[28]	3.0	*2.4*[a]	Not stated
Gambia Government–MRC Joint Ethics Committee[27]	*Range: 2.4 (e.g.1-kg infant) to 0.3 (e.g. 20-kg 4-year-old or 30-kg 9-year-old)*[a]	2, up to max 5 ml (age 0–4 yr); 10 ml (age 5–9 yr); 15 ml (age 10–14 yr); 30 ml (age ≥15 yr)	Within 3 months same as for one draw, "usually"

Hb, haemoglobin; IRB, institutional review board; ml/kg, millilitres per kilogram of body weight; MRC, Medical Research Council; TBV, total blood volume.
[a] Calculated on the basis of a TBV of 75–80 ml/kg (in neonates, 100 ml/kg). Non-italicised content is quoted directly from the sources.
[b] Provided by the KEMRI–Wellcome Trust Research Programme, Kilifi, Kenya, in October 2006 with an updated version provided to the author in August 2009. These are local practice guidelines reflecting the latest recommendations of this institution.