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CLINICAL PROTOCOL CV185362

A Prospective, Randomized, Open Label, Multi-center Study of the Safety and Pharmacokinetics of Apixaban versus Vitamin K Antagonist or LMWH in Pediatric Subjects with Congenital or Acquired Heart Disease Requiring Chronic Anticoagulation for Thromboembolism Prevention

Revised Protocol Number: 04

[redacted]

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	16-Jul-2020	• Neonates (subjects < 28 days of age) will no longer be included in the study • Randomization stratification will be reduced from four groups to three groups (will no longer include neonates) • Subjects < 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 1 month • Subjects ≥ 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 6 months • Subjects < 3 kg are excluded • Corrected PK/PD blood volumes for subjects < 3 months of age • Added separate blood sampling table for young infant subjects using dried blood spot technology for PK sampling
Revised Protocol 03	27-Jan-2020	• Open enrollment to patients 28 days to < 3 months and ≥ 3 kg • Add apixaban dose weight tiers for subjects > 3 kg to < 6 kg • Introduce apixaban 0.1 mg capsules for patients < 5 kg • Add a 6 week office visit for patients 28 days to < 3 months for weighing and adjustment of the apixaban dose • Update exclusion criteria for subjects with known inherited bleeding disorders, coagulopathies, and antiphospholipid syndrome • Introduce a PK blood collection method using dried blood spot technology for patients < 3 months of age at randomization • Replace 1.0 ml blood collection tube with a 1.4 ml blood collection tube which will result in an additional collection of 1) 1.6 ml of blood for children ≥ 1 year of age and 2) 3.2 ml of blood for children 3 months to < 1 year of age over the course of the whole study • Add a PK/PD sampling schedule for patients 28 days to < 3 months of age
Revised Protocol 02	07-Jun-2019	• Ensure that subjects are receiving the expected study treatment duration of 12 months • Definition of a month being changed from 28 days to 30 days. • Sample size is being increased by 50 patients to 200 to account for those patients who completed the study with less than one year treatment duration • Statistical tables have been revised to account for the increased sample size • Exclusion criteria was revised for those patients with a known inherited or acquired thrombotic disorder • Minor administrative changes will be incorporated
Administrative Letter 01	17-Sep-2018	Updated study personnel.
Revised Protocol 01	07-Dec-2017	Incorporates Amendment 03
Amendment 03	07-Dec-2017	• Introduce the study acronym ‘SAXOPHONE’

Document	Date of Issue	Summary of Change
		• Changed apixaban dosing scheme from a mg/kg dosing to a fixed-dose, body weight-tiered regimen • Introduced the 0.5 mg tablet with dosing instructions and dose selection rationale [redacted] • Opened up the younger age group to allow enrollment of children ≥ 3 months of age. • Indicated that only children ≥ 6 kg can be enrolled • Eliminated the 8 and 10 month phone visit and replaced with an optional 9 month site visit (mandatory office visit for children < 2 years of age. Office visit or phone visit for children ≥ 2 years of age) • Adjusted QOL assessment based on initiation of anticoagulation therapy • Previous anticoagulation: PedsQL and KIDCLOT at Day 1 visit. No assessment at Week 2 visit • Just starting anticoagulation: PedsQL at Day 1 Visit and KIDCLOT at Week 2 visit • Replaced Blood Pressure Tables with newly released tables contained within the AAP Clinical Practice Guidelines • Reduced total per day blood volume sampling by 1) moving sample points to different days and 2) reducing the blood volume for PK and antiXa activity assays for children < 1 year of age to 1 ml and [redacted] • Added to exclusion criteria confirmed diagnosis of a GI ulcer
Original Protocol	05-Oct-2016	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 04:

The main reason for revising the protocol is to remove the neonate cohort from the study population [redacted] and update the minimum treatment duration for subject under the age of 2 years.

The revised protocol applies to all future participants and to all participants currently enrolled.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Study Design	Remove neonate cohort from study population	[redacted] as indications for anticoagulation for primary prevention are extremely rare in neonates with cardiovascular diseases
Synopsis: Study Design	Remove neonates from randomization stratification	[redacted] as indications for anticoagulation for primary prevention are extremely rare in neonates with cardiovascular diseases
Synopsis: Study Population	Patients < 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 1 month	Adjusted age limits on anticoagulation requirements
Synopsis: Study Population	Patients ≥ 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 6 months	Adjusted age limits on anticoagulation requirements
Synopsis: Inclusion criteria	Remove neonates from study population	[redacted] as indications for anticoagulation for primary prevention are extremely rare in neonates with cardiovascular diseases
Synopsis: Exclusion criteria	Exclude subjects < 3 kg	Define minimum weight limit

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis: Table 1.3	Correct whole blood volume for PK/PD in children < 3 months of age	Correction
Synopsis: Table 1.4	Sampling Schedule for PK using dried blood spot sampling	Clarify blood sample schedule if using dried blood spot technology
Body: Section 3.1 Study Design and Duration	Remove neonates from study population	[redacted] as indications for anticoagulation for primary prevention are extremely rare in neonates with cardiovascular diseases
Body: Section 3.1 Study Design and Duration	Patients < 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 1 month	Adjusted age limits on anticoagulation requirements
Body: Section 3.1 Study Design and Duration	Patients ≥ 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 6 months	Adjusted age limits on anticoagulation requirements
Body: Section 3.3 Study Population	Defined population to include children 28 days to < 18 years of age and weighing > 3 kg	Clarified study population
Body: Section 3.3 Study Population	Patients < 2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 1 month	Adjusted age limits on anticoagulation requirements
Body: Section 3.3 Study Population	Patients ≥2 years of age at the time of randomization should be expected to require anticoagulation for a minimum of 6 months	Adjusted age limits on anticoagulation requirements

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Body: Section 3.3.1 Inclusion criteria, #3 Age and Reproduction Status	Defined population to include children 28 days to < 18 years of age	Clarified study population
Body: Section 3.3.2 Exclusion criteria, #3 Physical and Laboratory Test Findings	Excluded children < 3 kg	Define weight limits
Body: Table 5.5-3	Correct whole blood volume for PK/PD in children < 3 months of age	Correction
Body: Table 5.5-4	Sampling Schedule for PK using dried blood spot sampling	Clarify blood sample schedule if using dried blood spot technology
Appendices: Appendix 1, Table 3	Correct whole blood volume for PK/PD in children < 3 months of age	Correction
Appendices: Appendix 1, Table 3	Sampling Schedule for PK using dried blood spot sampling	Clarify blood sample schedule if using dried blood spot technology
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

SYNOPSIS

Clinical Protocol CV185362

Protocol Title: A Prospective, Randomized, Open Label, Multi-center Study of the Safety and Pharmacokinetics of Apixaban versus Vitamin K Antagonist or LMWH in Pediatric Subjects with Congenital or Acquired Heart Disease Requiring Chronic Anticoagulation for Thromboembolism Prevention

Study Acronym: SAXOPHONE Safety of ApiXaban On Pediatric Heart disease On the preventioN of Embolism

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product

Children aged 28 days to < 18 years of age are eligible for the study. Children randomized to the apixaban arm of the study weighing between ≥ 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2 mg and 4 mg depending on body weight using the 0.1 mg capsules and 0.5 mg mini-tablets. Instructions will be provided on how to dissolve the 0.1 mg capsules and suspend the mini-tablets into solution. Alternatively, children ≥ 5 years will have the option of using the oral solution formulation at the same doses as would be recommended for the mini-tablet formulation. Note that children < 5 years of age will not have the option of being dosed via the oral solution formulation.

Children randomized to the apixaban arm of the study weighing ≥ 35 kg will be administered apixaban 5 mg twice daily (BID) as a tablet or with the oral solution.

Apixaban doses can be administered by mouth (PO) or via a nasogastric tube (NGT) or gastric tube (GT) followed with or without food approximately 12 hours apart. The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor. The apixaban 5 mg tablet can be crushed and suspended in water or 5% dextrose in water (D5W) or apple juice or can be mixed with applesauce and promptly administered orally. Alternatively, apixaban 5 mg tablets can be crushed and suspended in 60 mL of water or D5W and promptly delivered through an NGT. The apixaban 0.5 mg tablets can be mixed with applesauce or can be dissolved in water, apple juice, or formula and promptly administered orally or via NGT/GT. Apixaban should not be administered through a nasojejunal tube (NJT)/post-pyloric feeding tube due to decreased absorption.

Either apixaban or active comparators will be started according to the guideline recommended time after randomization when the subjects are able to tolerate oral or enteral intake, and treatment will be continued for up to 12 months or until the need for anticoagulant is resolved, whichever is shorter. At the end of the study, all subjects will be converted to the standard of care (SOC). Drug diaries will be used to record administration of study medication.

During the study, apixaban treatment will be held at least 24 hours prior to any planned elective surgery or invasive procedures. Apixaban should be resumed after the procedure when adequate hemostasis has been established but no sooner than 24 hours after the procedure, and no later than 10 days after the procedure. Bridging strategies with unfractionated heparin (UFH) are permitted in the interim, per local institutional practices. Dose interruption for vitamin K antagonists (VKA) and low molecular weight heparin (LMWH) will follow the local institutional standard practice informed by the ACCP (American College of Chest Physicians) 2012 guideline and the local product label for thromboembolism prophylaxis. Subjects who receive LMWH are allowed to switch to VKA at any time during the study; conversely, subjects having difficulty with VKA may switch to LMWH.

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL. Exact targets may vary by condition and local standard of care.

Study Phase: Phase II

Research Hypothesis:

The study will generate safety, pharmacokinetics (PK), pharmacodynamics (PD), quality of life (QOL), [redacted] exploratory efficacy data to inform clinicians regarding apixaban dosing and management of thromboprophylaxis in pediatric subjects with congenital or acquired heart disease requiring chronic prophylactic

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:

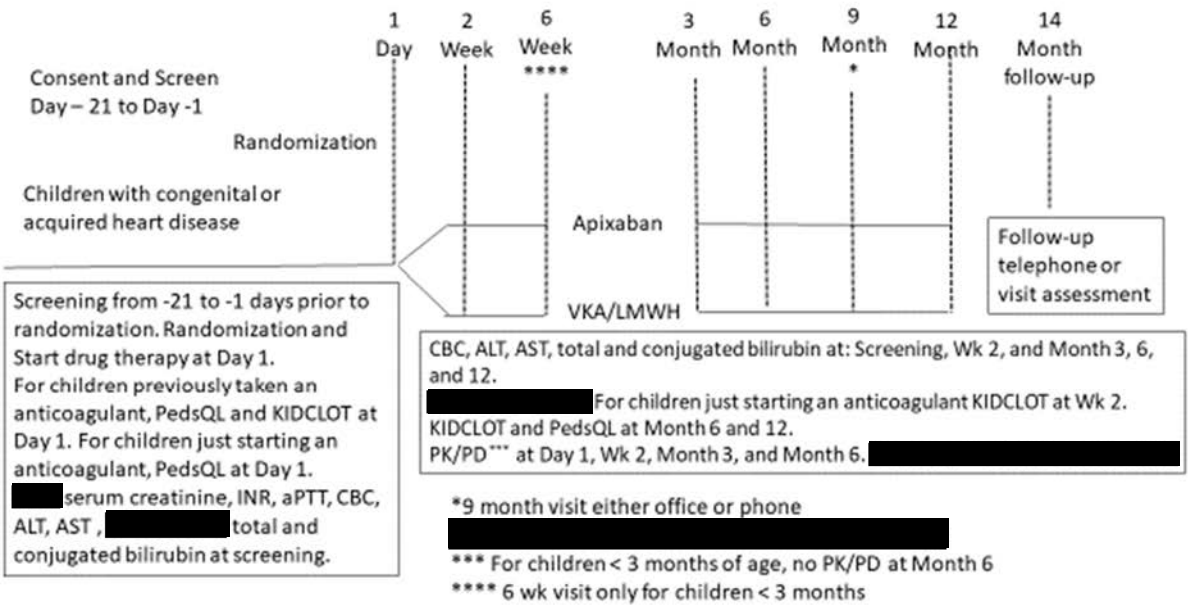
[redacted] Recruitment started in January 2017 for children of ages ≥ 2 to < 18 years, and was subsequently expanded to ≥ 3 months in December 2017. Enrollment was further expanded in February 2020 to subjects ages 28 days to < 3 months. Neonates will no longer be included in the study population [redacted].

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.

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.

Key Inclusion Criteria:

1. Males and females, 28 days to < 18 years of age
2. 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 there is evidence (by previously obtained clinical imaging data) for thrombus stability or resolution.
3. Eligible subjects include those who newly start anticoagulants and those who are currently on VKA or LMWH or other anticoagulants for thromboprophylaxis.
4. Able to tolerate enteral medication [e.g., by mouth, Nasogastric (NGT) tube, or Gastric-(GT) tube]
5. Subjects 28 days to < 3 months at the time of randomization must be able to tolerate oral/NGT/GT feeds for at least five days

Key Exclusion Criteria:

1. Thromboembolic events less than 6 months prior to enrollment
2. Use of aggressive life-saving therapies such as ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) at the time of enrollment
3. Artificial heart valves or mechanical heart valves

   Note: These materials are not an exclusion: allograft/homograft valves and tissue valves; prosthetic material in the vascular system such as shunts, patches and polytetrafluoroethylene (PTFE) baffle or other prosthetic material.
4. Active bleeding at the time of enrollment
5. Known inherited bleeding disorder or coagulopathy (e.g., hemophilia, von Willebrand disease, etc)
6. Known intracranial congenital vascular malformation or tumor
7. Any major bleeding other than perioperative in the preceding 3 months
8. Confirmed diagnosis of a GI ulcer
9. Uncontrolled severe hypertension (> 99th percentile of systolic or diastolic blood pressure by AAP Clinical Practice Guidelines) (Appendix 2)
10. Liver dysfunction (e.g., ALT > 3X ULN and/or AST > 3X ULN and/or direct [conjugated] bilirubin 2X ULN without an alternative causative factor such as Gilbert's syndrome or Dubin-Johnson syndrome
11. Renal function < 30% of normal for age, gender, and height as determined by the Schwartz formula: (GFR [mL/min/1.73m2] = [0.413 x height (cm)] / serum creatinine (mg/dL) (Appendix 5)
12. Platelet count < 50,000/uL
13. In the opinion of the Investigator, it is not possible for the subject to be compliant with the protocol and study procedures
14. Pregnancy during the study period
15. Concurrent use of or participation in another experimental drug/device trial
16. Known antiphospholipid syndrome [APS]
17. Weight < 3 kg

If a subject becomes ineligible for the study drug during the study, (e.g., receives a VAD, ECMO, or a heart transplantation), study drug must be discontinued, and treatment should be converted to the SOC per guidelines (e.g., ACCP 2012 guideline). Perioperative use of cardiopulmonary bypass (CPB) is not an exclusion; however, apixaban treatment should be interrupted during CPB as described in section 4.5.2, and intermittent anti-coagulation (e.g., UFH) should be used per current guideline recommendations (ACCP 2012 guideline).

Prohibited Therapies and/or Medications:

- Non-study related concurrent prophylactic or therapeutic treatment with LMWH, UFH, other oral anticoagulant, or systemic thrombolytic. Heparin flushes to maintain Central Venous Access Device (CVAD) patency and local tissue plasminogen activator (tPA) to restore CVAD patency are permitted. UFH and LMWH may be used as part of a bridging strategy
- Dual anti-platelet therapy or mono anti-platelet therapy with thienopyridines such as clopidogrel, ticagrelor, or prasugrel (low-dose aspirin is allowed for some conditions such as Kawasaki disease and single ventricle physiology, but aspirin > 5 mg/kg per day will have to be discussed with and approved by the medical monitor)
- Concomitant systemic treatment with strong inhibitors that inhibit both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, clarithromycin, and ritonavir; concomitant systemic treatment with strong inducers of both cytochrome P450 3A4 and P-gp such as rifampin, phenytoin, and carbamazepine (Appendix 3)

Note: Less potent CYP 3A4 and P-gp inhibitors such as fluconazole, voriconazole, topical azole antifungal agents, H2-antagonists and proton pump inhibitors are permitted.

Chronic daily use of nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., naproxen, ibuprofen, diclofenac, etc) may increase the risk of bleeding. Therefore, concomitant use of NSAIDS for more than one consecutive month after randomization is prohibited (Appendix 4).

During the entire study period, no other investigational agents, other than apixaban should be administered to the subject.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CV185362		
Medication	**Potency**	**IP/Non-IP**
BMS-562247-01 Capsule 0.1 mg	0.1 mg	IP
BMS-562247-01 Film Coated Tablet 0.5 mg	0.5 mg	IP
BMS-562247-01 Film Coated Tablet 5 mg	5 mg	IP
BMS-562247-01 Oral Solution 0.4 mg/mL	0.4 mg/ml	IP
Warfarin (or other VKA)	1, 2.5, and 5 mg	IP
Enoxaparin sodium	100 mg/mL	IP
Enoxaparin sodium (Clexane)	100 mg/mL	IP

Study Assessments:

There will be 3 study periods extending up to 14 months. 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 (or when anticoagulation is no longer needed) to two months later.

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 the Interactive Web Response System (IWRS) will be contacted to obtain a unique subject number. 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 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. A complete medical history and a physical examination including vital signs (heart rate, respiratory rate, blood pressure, body 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), aPTT, and INR 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.

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 randomization visit. Drug diaries will be used to record administration of study medication.

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 screening visit as part of standard of care or during the screening visit) that are 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 Appendix **Table 1** in the protocol for details). [redacted]

Revised Protocol 03 introduced dried blood spot (DBS) as a blood volume conserving collection method for PK in subjects < 3 months at the time of randomization.

[redacted]

Quality of Life (QOL) instruments will be given to 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.

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. 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. The timing of these study visits will coincide as much as possible with standard-of-care visits for these pediatric subjects. Visits will consist of clinical evaluation of thromboembolic events, bleeding events, reporting AEs, therapeutic monitoring (INR for VKA or anti-Xa activity for LMWH), monitoring medication adherence, safety laboratory studies (CBC, ALT, AST, total and conjugated bilirubin), serum or urine pregnancy test for WOCBP and concomitant therapy assessment for all enrolled subjects. Subjects on VKA or LMWH may have additional visits as needed for adjustment of their dose and monitoring at the discretion of the investigator and/or treating physician. PK/PD samples will be drawn at Day 1, Week 2, Month 3, and Month 6. No PK/PD samples will be drawn at the 6 month visit for subjects < 3 months of age. [redacted] PK/PD [redacted] samples will be analyzed at a central core laboratory. Safety labs will be analyzed locally.

The subject's weight will be measured at the 3, 6 (subject 28 days to < 3 months of age), 9, and 12 month visit. A 6 week visit is mandatory for subjects < 3 months of age at randomization. A 9 month office visit is mandatory for subjects < 2 years of age or can be either an office visit or phone visit for subjects ≥ 1 year of age, and the apixaban dose should be adjusted based on body weight changes according to the dosing guidance document that will be provided to each site.

[redacted]

Quality of Life 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. Additionally, the KidsClot Quality of Life instrument will be administered at the Week 2 visit only if the subject is just starting an anticoagulant (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 **Follow-up Period**, a 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. Subjects will be instructed to report all AE to the investigator, including those symptoms suggestive of occurrence of thrombosis or bleeding.

Early drug discontinuation: all subjects who discontinue study drug prior to the Month 12 visit should complete their end-of-study evaluation (e.g., QOL, [redacted] other laboratory tests, etc.) at the time of drug discontinuation + 2 weeks and have a telephone or in-person safety assessment 2 months thereafter. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Imaging Evaluation:

[redacted]

Routine mandatory imaging for thromboembolic events is not required for the study. However, any clinical, radiologic and catheter evaluations prompted by clinical suspicion of any thromboembolic events, bleeding or death should 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.

Dose Selection:

Additional PK data for children aged 14 days to < 3 months of age together with previous PK data were used to support the dose selection rationale for pediatric subjects aged 28 days to < 18 years. Based on PK simulations performed with a well-developed PPK model, a dosing scheme has been selected for the age cohort to be enrolled (28 days [and ≥ 3 kg] to < 18 years).

With the introduction of 0.5-mg tablets, the dosing paradigm of apixaban changed from mg/kg dosing to fixed-dose, body weight-tiered regimen, as outlined in the table below. The fixed-dose, body weight-tiered regimen for pediatric subjects at least 6 kg and 3 months of age or older, used apixaban doses in increments of 0.5 to 1 mg according to the appropriate weight range, for both oral solution and 0.5-mg tablets. With the introduction of the 0.1 mg capsule formulation, a body weight-tiered dosing regimen will continue for subjects ≥ 3 kg and as young as 28 days of age. Increments are now reduced to 0.1 mg. The modelling and simulation results support the current dosing recommendation of fixed-dose body weight-tiered regimen for pediatric subjects aged 28 days to < 18 years.

Apixaban will be administered in accordance with the dosing instructions provided in separate documents and in the table below. For subjects who are currently on the mg/kg dosing regimen, their dosing will be switched to the fixed-dose, body weight-tiered regimen at their next scheduled visit

Apixaban Doses for Ages 28 Days to < 18 Year		
Weight range	**Dose**	**Apixaban Formulation***
3 to < 4 kg	0.2 mg twice daily	0.1 mg capsules
4 to < 5 kg	0.3 mg twice daily	0.1 mg capsules
5 to < 6 kg	0.5 mg twice daily	0.5 mg tablets
6 to < 9 kg	1 mg twice daily	0.5 mg tablets
9 to < 12 kg	1.5 mg twice daily	0.5 mg tablets
12 to < 18 kg	2 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
18 to < 25 kg	3 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
25 to < 35 kg	4 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
≥35 kg	5 mg twice daily	5 mg tablet or 0.4 mg/ml oral solution

*For children < 5 years available formulations include 0.1 mg capsules or 0.5-mg tablets

The 0.4 mg/ml solution cannot be used in children < 5 years

For children ≥ 5 years available formulations include 0.5-mg tablets, 5 mg tablets (only if body weight ≥ 35 kg), or 0.4 mg/ml oral solution

PK/PD Samples [redacted]:

Samples for PK, PD (Chromogenic FX assay), and anti-FXa activity 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.

[redacted]

Tables 1-1 to 1-4 summarizes the sampling collection schedule. Attempts should be made to coordinate blood sampling with the blood draw for safety labs

Table 1.1: 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 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] For subjects who discontinue treatment 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]

Table 1.2: Sampling Schedule for PK and PD for Children 3 Months to < 1 Year 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 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

[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).

Table 1.3: 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 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.

[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).

Table 1.4: 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 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.

[b] For subjects undergoing surgery and possibly getting a transfusion, the PK 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

Statistical Considerations:

Sample Size:

The reported low incidence of thromboembolic and bleeding events in children limits the feasibility for a phase III trial by requiring an excessively high sample size. 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 current study is designed to characterize apixaban safety and PK/PD profile, and is a descriptive study for which the safety, PK/PD, and efficacy variables will be summarized.

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. The observed 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 (see section 8.1 of the protocol for details).

Endpoints:

Primary Endpoints:

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 clinically relevant non-major (CRNM) bleeding events per the Perinatal and Paediatric Haemostasis Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) criteria. Bleeding definitions are described as follows:

Major **bleeding** is defined as bleeding that satisfies one or more of the following criteria:

- fatal bleeding
- 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
- bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS
- bleeding that requires surgical intervention in an operating suite, including interventional radiology

CRNM bleeding is defined as bleeding that satisfies one or both of the following criteria:

- overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition
- bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room

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

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).

Secondary Endpoints:

Pharmacokinetics:

Apixaban PK will be characterized using a population PK approach. Nonlinear mixed effects modeling will be used to estimate population and individual pharmacokinetic 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.

PK/PD (measuring FX using chromogenic assay), anti-FXa activity, as well as exposure-response (E-R) relationships, may be explored.

Efficacy:

1. 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.

   All thromboembolic events and death will be adjudicated by a blinded, independent adjudication committee.

2. Patient/proxy reported outcome or quality of life (e.g., PedsQL generic core and cardiac modules, and KIDCLOT©)

Safety:

1. Adjudicated major bleeding
2. Adjudicated CRNM bleeding
3. All bleeding
4. Drug discontinuation due to adverse effects, intolerability, or bleeding
5. All cause death

Analyses:

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's method if applicable. Analytic methods for secondary [redacted] endpoints will be provided in the protocol.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

1.1.1 Clinical Problem and Unmet Need

Children with congenital or acquired heart disease are at risk for clinically significant thrombosis, including intracardiac, intravascular, and coronary thromboses; thrombosis of surgically-placed shunts; and thromboembolic stroke. Thrombosis complications are increasingly recognized as important factors contributing to the morbidity and mortality in these disease populations.[1,2,3] Hemodynamic factors related to abnormal ventricular function, arrhythmias, catheterization and complex cardiac anatomy are important contributors to the risk of thrombosis.

The highest risk groups include children with congenital heart disease of the single ventricle type in whom all of these factors may co-exist.[3, 4] In observational cohort studies, the period prevalence of thrombotic complications has been reported to be 40% after initial palliation and 28% after superior cavopulmonary connection (SCPC),[4] whereas in a large randomized clinical study, the incidence of composite death and thrombotic complications during a median follow up duration of 5.8 months after initial palliation was noted to be approximately 20%.[5] The prevalence of clinically-evident thrombotic events was reported to be 7% during two years after the Fontan procedure and increased to as high as 20% when including asymptomatic thrombosis identified by transesophageal echocardiogram.[6]

In children with acquired heart diseases, high-risk groups for thrombosis include dilated cardiomyopathy and Kawasaki disease with coronary artery aneurysms. Retrospective review[7,8,9] of pediatric patients with dilated cardiomyopathy suggests an incidence of thrombus/embolism ranging from 1 to 16%, likely related to low cardiac output or focal ventricular wall motion abnormalities, leading to localized stasis. Kawasaki disease, if untreated, may result in coronary artery aneurysms in 20% to 25% of affected children and may lead to ischemic heart disease or sudden death.[10] However, the prevalence of coronary artery aneurysms is reduced to < 5% by administration of high-dose intravenous immune globulin within 10 days of fever onset[10]. Event rates for thrombotic complications in patients with Kawasaki disease and giant aneurysms treated with aspirin alone or in combination with an anticoagulant vary from 0.5 to 2.7 events per 100 patient-years.[11] Low cardiovascular event rates of 0.246 per 1000 person-years were reported in a recent US cohort study of 546 patients with Kawasaki disease who were followed for cardiovascular outcomes over 14.9 years post-diagnosis.[12]

Other high risk groups[1,13] include children with prosthetic heart valves, pulmonary hypertension, other forms of complex congenital heart diseases, and those who require transvenous pacing systems.

Despite a better understanding of the risk factors, there continues to be sparse data regarding the optimal strategies for prevention, detection, and management of thrombosis in pediatric heart disease.[2] Many of the standard drugs (e.g., warfarin, low-molecular-weight heparin [LMWH],

and heparin) are used variably at different doses, and are often being used off label.[13,14] The agents studied most frequently in children (heparin, and LMWH) are associated with unwanted adverse effects such as potential decrease in bone mineral density[15] and heparin-induced thrombocytopenia,[15,16] and have the disadvantages of requiring parenteral administration and therapeutic monitoring. Further, heparins require antithrombin III for an adequate effect, and antithrombin III levels are frequently low and variable in neonates and other sick children. Direct Factor Xa (FXa) inhibitors that do not require antithrombin III, may be a better option for these patients. Warfarin and other vitamin K antagonists (VKAs) like warfarin suffer from a number of shortcomings as well, including a narrow therapeutic window, the need for therapeutic monitoring, potential drug-drug and drug-food interactions, and the lack of an oral pediatric formulation. Therefore, the current standard anticoagulants are associated with sub-optimal benefit/risk ratio and acceptability, as demonstrated in a recent randomized trial, and lead to poor compliance, adherence, and therapeutic effect.[6]

Although the AHA Scientific Statement[1] and the American College of Chest Physicians[13] have provided clinical practice guidelines for pediatric thrombosis, the majority of recommendations are based upon consensus opinion in the absence of randomized clinical trials (that is, Level 2C evidence). Thus, almost two decades after the first randomized clinical trial of anticoagulation in children for venous thromboembolism (VTE), the level of evidence on which current therapy is based has not progressed. This highlights the need for alternative and novel strategies to increase the safety and efficacy of anticoagulation of children.[2] Additionally, there remains a pressing need for the availability and improved understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of novel anticoagulants with age-appropriate pediatric formulations and without the drawbacks of LMWH or VKAs. The advent of new oral anticoagulants (NOACs) such as direct FXa inhibitors (e.g., apixaban) provides an opportunity to address these needs, and trials in children with NOACs have been identified as a high priority research aim by a group of experts.[2]

Apixaban (BMS-562247) is a novel, orally active, direct inhibitor of FXa that binds to the active site of FXa without requiring antithrombin III. Apixaban has been studied in more than 20 randomized clinical trials in over 60,000 subjects in the adult clinical development program for various indications,[17,18,19,20,21] and has demonstrated a favorable benefit-risk profile. Apixaban has been approved for stroke prevention in non-valvular atrial fibrillation (NVAF), prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery, and for the treatment and reduction of the risk of recurrence of VTE in adult patients. Apixaban is expected to have advantages over currently available antithrombotic agents used for the prevention and treatment of arterial and venous thrombosis. As an oral agent with a liquid formulation, apixaban is more convenient to administer than parenteral agents (e.g, unfractionated heparin, enoxaparin, and fondaparinux), especially in subjects requiring prolonged treatment. Furthermore, unlike VKAs, apixaban has predictable dosing with low inter-subject variability, is not expected to require monitoring of coagulation markers or dose adjustment, and is not expected to have significant interactions with food, drugs or botanical

products. Thus, apixaban could be a new option as a safe, pediatric friendly anticoagulant for prevention of thromboembolism (TE) in children with heart disease.

Accordingly, the Sponsor (Bristol-Myers Squibb [BMS]) is undertaking the present randomized, open-label, parallel-arm Phase II study using the standard of care (SOC, e.g., VKA antagonist or subcutaneous LMWH) as an active comparator, to establish the safety and PK of apixaban in the prevention of TE in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation. The study will include pediatric subjects congenital heart disease, as well as subjects with acquired heart disease who require long-term anticoagulation for thromboprophylaxis. The rationale for including a broad range of congenital and acquired heart disease is the high unmet medical need in these populations, and because small numbers of patients at risk for each disease type makes studying a population with a single ventricle disease alone extremely challenging.[2]

The current randomized Phase II trial will enroll pediatric subjects with acquired and congenital heart disease who require chronic anticoagulation for thromboprophylaxis. Subjects will be randomized to receive apixaban versus VKA or subcutaneous LMWH. Findings from the trial will provide important information including apixaban safety, dosing guidance and quality of life (QOL) across different age groups in a broad pediatric heart disease population.

1.1.2 Rationale for Dose

In Phase 3 studies for adult patients (ARISTOTLE trial)[17] 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 would result in a favorable safety and efficacy profile in this pediatric population. Therefore, the proposed dose for this study is targeted to achieve a plasma exposure that is similar to the exposure in the adult stroke prevention trial ARISTOTLE. Exposures for this subset of patients are consistent with exposures observed in the VTE treatment population for those patients dosed with 5 mg BID. Based on population pharmacokinetic (PPK) modeling of younger subjects in this Phase 3 NVAF 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 twice daily (BID) dosing regimen, thus the target exposure used to drive dose selection for this protocol was half this value, which is equal to the steady state exposure over one dosing interval, AUC(TAU), of 1200 ng*hr/mL As a consequence of the change to solid dose formulations for children < 5 years of age, prompted by a revision of the EMA guidance for propylene glycol excipient use, a weight tiered dosing scheme was developed. This dosing scheme achieves comparable exposures to the weight based scheme that was used initially to support dose selection.

Children aged 28 days to < 18 years of age are eligible for the study. Children randomized to the apixaban arm of the study weighing between 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2 mg and 4 mg depending on body weight using the 0.1 mg capsules and 0.5 mg tablets. Instructions will be provided on how to dissolve the 0.1 mg capsules and suspend the mini-tablets into solution/suspension. Alternatively, children ≥ 5 years will have

the option of using the oral solution formulation at the same doses as would be recommended for the 0.5 mg tablet formulation.

Children randomized to the apixaban arm of the study weighing ≥ 35 kg will be administered apixaban 5 mg twice daily (BID) as a tablet or solution. Note that children < 5 years of age will not have the option of being dosed via the oral solution formulation.

Apixaban can be administered by mouth (PO) or via a NGT or GT approximately 12 hours apart, followed with or without food. The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor. The apixaban 5 mg tablet can be crushed and suspended in water or 5% dextrose in water (D5W) or apple juice or can be mixed with applesauce and promptly administered orally. Alternatively, apixaban 5 mg tablets can be crushed and suspended in 60 mL of water or D5W and promptly delivered through an NGT. The apixaban 0.5 mg tablets can be mixed with applesauce or can be dissolved in water, apple juice, or baby formula and promptly administered orally or via NGT/GT. Apixaban should not be administered through NJT/post-pyloric feeding tubes due to decreased absorption. The apixaban 0.1 mg capsules will need to be opened and dissolved in infant formula or breast milk and promptly administered orally or via NGT/GT.

The dose of apixaban was determined by a model-based approach, using a PPK modeling method. Briefly, a PPK model was developed using available data from apixaban pediatric PK/PD studies in children aged 14 days to 18 years (CV185118 and CV185079) pooled with adult data (children down to 28 days). Apixaban exposure was adequately characterized by a 2-compartment model with first order absorption and first order elimination with the primary influential covariate of body weight for scaling of clearance (CL) and volume (V) in this patient population. Based on PK simulations performed with this model a weight-based dosing scheme was previously selected for the initial age cohort to be enrolled (2 to < 18 years). Subsequent analysis supported a weight-based scheme for children down to 3 months of age. The most recent analysis, provides dose recommendations in support of enrollment of patients down to 28 days of age based on additional PK data in young infants that are now available.

Simulations showed that this proposed dosing scheme achieved a similar median steady-state area under the concentration-time curve in one dosing interval AUC(TAU) in this population to that observed in adults in the stroke prevention trial who received apixaban. This approach to dose selection has been used to identify pediatric doses for two additional studies: 1) the study exploring the safety and efficacy of apixaban for TE prevention during induction chemotherapy in children with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoma (T- or B-cell) treated with asparaginase, and 2) the study evaluating apixaban in pediatric subjects requiring anticoagulation for the treatment of VTE events.

[redacted] As such, recruitment started in January 2017 with children of ages 2- < 18 years and was subsequently expanded to > 3 months in children weighing > 6 kg in December 2017. The same model-based approach targeting median Adult AUCs was used to select doses for infants ages 28 days to < 3 months weighing ≥ 3 kg. The

model has been updated with the data from the pediatric PK/PD study and simulations were performed to identify the dose that best achieves the target AUC. Upon each update, sites and their respective IRBs are notified of the dosing recommendation for each cohort of children to be enrolled. Enrollment was expanded accordingly to subjects ages 28 days to < 3 months through a protocol amendment in January 2020.

1.2 Research Hypothesis

The study will generate safety, PK, PD, QOL, [redacted] and exploratory efficacy data to inform clinicians regarding apixaban dosing and management of thromboprophylaxis in pediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation. When compared with VKA antagonists or subcutaneous LMWH, apixaban is expected to be safe, and may improve QOL in the study population.

1.3 Objectives

1.3.1 Primary Objectives

To assess the safety of apixaban, compared to VKA or subcutaneous LMWH and to evaluate apixaban PK in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

1.3.2 Secondary Objectives

In pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis:

- To assess apixaban PD by measuring FX using chromogenic assay and anti FXa activity
- To compare the effects of apixaban on QOL measures versus VKAs antagonists or subcutaneous LMWH
- To gather exploratory data on the efficacy of apixaban

[redacted]

1.4 Product Development Background

Apixaban has undergone comprehensive clinical and nonclinical testing. Detailed summaries of the pharmacology, absorption/distribution/metabolism/excretion (ADME), toxicology and clinical experience with apixaban are provided in the Investigator Brochure and apixaban product label. The following paragraphs briefly summarize apixaban toxicology, PK and safety characteristics.[22,23]

Apixaban is a potent and selective inhibitor of coagulation FXa in vitro and in vivo. The toxicity of apixaban in animals was comprehensively evaluated in a spectrum of International Conference of Harmonization (ICH) and Good Laboratory Practice (GLP) compliant studies including

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.

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

Factor X concentrations in neonates and infants, the inhibitory effect of apixaban on FXa in pediatrics appeared to be generally consistent with the effect observed in adults. Specifically, relative to the effect observed in adult plasma, apixaban at 110 ng/mL, resulted in 17%, 16%, and 21% greater inhibition of FXa in infant, neonate, and umbilical cord blood plasma, respectively.

Study CV185079 evaluated the multiple-dose PK, PD, safety and tolerability of apixaban in 8 pediatric subjects up to 18 years of age with an indwelling central venous catheter. Though the study was terminated early due to poor enrollment, 6 subjects between the ages of 13 to 17 were administered 0.66 mg/m2 apixaban twice daily for 10 days and 2 subjects ages 6 and 11 were administered 0.60 mg/m2 apixaban twice daily for 10 days. Model-estimated steady state AUC(TAU) was 234.6 ng/mL and 223.5 ng/mL in the pediatric subjects between 13-17 years and 6-11 years of age, respectively. Apixaban was generally safe and well-tolerated by all 8 subjects in this study. There were no deaths, treatment-related serious adverse events (SAEs), or bleeding-related adverse events (AEs) reported. The most frequently occurring AEs and laboratory marked abnormality was prolonged aPTT. Prolongation of aPTT is a known pharmacological effect of direct acting Factor Xa inhibitors and as noted above, aPTT prolongation was not associated with any bleeding events in the study. Apixaban administration had no apparent impact on vital signs or physical examination findings.

Study CV185118 is a single-dose study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As of June 2019, a total of 47 subjects received apixaban and were included in the current dose selection: 10 subjects 12 years to <18 years of age, 10 subjects 6 years to <12 years of age, 8 subjects 2 years to <6 years of age, 9 subjects 9 months to <2 years of age, and 9 subjects 28 days to <9 months of age and 1 subject <28 days of age.

To date, apixaban has been well tolerated, and there have been no significant apixaban-related safety findings in CV185118. The results of this analysis showed that the clearance of orally administered apixaban increased with increasing age and reached values similar to those of adults in pediatric subjects older than 12 years. In addition, oral clearance, when normalized to body weight, was constant across the pediatric age range of 3 months to 18 years, with a trend towards age dependence on clearance in infants < 3 months of age. The results of this analysis were used to support the dose selection rationale for pediatric subjects aged 28 days to < 18 years. A linear relationship between apixaban concentration and anti-FXa activity was observed, consistent with that observed in adult subjects. Based on PK simulations performed with this model a dosing scheme has been selected for the age cohort to be enrolled (28 days to < 18 years).

[redacted]

Apixaban Dose Selection

With the introduction of 0.5-mg tablets, the dosing paradigm of apixaban changed from mg/kg dosing to fixed-dose, body weight-tiered regimen, as outlined in Table 1.4-1. The fixed-dose, body weight-tiered regimen for infants and children at least 6 kg and 3 months of age or older uses apixaban doses in increments of 0.5 to 1 mg according to the appropriate weight range, for both oral solution and 0.5-mg tablets. With the introduction of the 0.1 mg capsule formulation, a body weight-tiered dosing regimen will continue for subjects ≥ 3 kg and as young as 28 days of age. Increments are now reduced to 0.1 mg. The modelling and simulation results, support the current dosing recommendation of fixed-dose body weight-tiered regimen for pediatric subjects aged 28 days to < 18 years.

Apixaban will be administered in accordance with the dosing instructions provided in separate documents and in Table 1.4-1. For subjects who are currently on the mg/kg dosing regimen, their dosing will be switched to the fixed-dose, body weight-tiered regimen at their next scheduled visit.

Table 1.4-1: Apixaban Doses for Ages 28 Days to < 18 Years

Weight range	Dose	Apixaban Formulation*
3 to < 4 kg	0.2 mg twice daily	0.1 mg capsules
4 to < 5 kg	0.3 mg twice daily	0.1 mg capsules
5 to < 6 kg	0.5 mg twice daily	0.5 mg tablets
6 to < 9 kg	1 mg twice daily	0.5 mg tablets
9 to < 12 kg	1.5 mg twice daily	0.5 mg tablets

Table 1.4-1: Apixaban Doses for Ages 28 Days to < 18 Years

Weight range	Dose	Apixaban Formulation*
12 to < 18 kg	2 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
18 to < 25 kg	3 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
25 to < 35 kg	4 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
≥35 kg	5 mg twice daily	5 mg tablet or 0.4 mg/ml oral solution

*For children < 5 years available formulations include 0.1 mg capsule or 0.5-mg tablets

For children < 5 years the 0.4 mg/ml oral formulation cannot be used

For children ≥ 5 years available formulations include 0.5-mg tablets, 5 mg tablets (use only if body weight ≥ 35 kg), or 0.4 mg/ml oral solution

The current randomized Phase II trial will enroll pediatric subjects with acquired and congenital heart disease who require chronic anticoagulation for thromboprophylaxis. Subjects will be randomized to receive apixaban versus VKA or subcutaneous LMWH. Findings from the trial will provide important information including apixaban safety, dosing guidance and QOL across different age groups in a broad pediatric heart disease population.

1.5 Overall Risk/Benefit Assessment

Potential benefits to subjects

As demonstrated in a number of clinical studies, apixaban has potent, predictable and lasting anticoagulant activity and a well behaved PK profile. Distinct features of apixaban include direct binding to the active site of FXa without requiring antithrombin III, a pediatric oral dosing formulation with consistent absorption and no food effect, lack of drug-drug interaction with other medications, no need for therapeutic monitoring, and a low risk of bleeding. These features may make it superior to currently available antithrombotic agents for thromboprophylaxis in children with acquired or congenital heart disease, thus addressing an unmet clinical need.

All patients are expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes multiple clinic visits, physical and laboratory examinations over the course of the study.

Potential risks

The primary liability for apixaban, as well as any anticoagulant, is undesired bleeding. Based on safety data obtained in the adult clinical program from over 60,000 subjects and post marketing experience from over 4 million adult patients worldwide, apixaban's risk of bleeding is expected to be low, and comparable to that of subcutaneous LMWH. While apixaban's risk of bleeding has been demonstrated to be lower than warfarin (ARISTOTLE),[8] it is interesting to learn that in patients undergoing invasive procedures while taking apixaban, the rates of post-procedural

major bleeding and death were low whether apixaban was interrupted or continued; whereas in patients taking warfarin, the rates of post-procedural major bleeding and death were at least 2-fold higher among those who continued warfarin versus those who interrupted treatment.[28]

Protection against risks

To minimize the risk of bleeding, subjects with known inherited bleeding tendencies or acquired coagulopathies will be excluded from the study. Study subjects will be closely monitored for any bleeding and thromboembolic events and for overall safety. Study treatment will be held for clinically significant bleeding. All bleeding events will be adjudicated by an independent Event Adjudication Committee (EAC), and the conduct of the trial will be supervised by an independent Data and Safety Monitoring Board (DSMB) run by the National Heart, Lung, and Blood Institute at the National Institutes of Health. The DSMB will have the responsibility to review the incidence of bleeding and thromboembolic events and the Chair of the DSMB (along with the Pediatric Heart Network (PHN) leadership and the Sponsor) will be provided with reports of SAEs on a regular basis. The DSMB may recommend modification or suspension of the trial for safety reasons.

In addition to DSMB supervision, the sponsor will conduct real-time monitoring and will review all safety information from all ongoing apixaban pediatric studies as they become available. Frequent safety signal detection will be performed, which will include integration of clinical study data, post marketing surveillance AE reports, pre-clinical data, epidemiological studies and literature reports, to identify and characterize unrecognized safety risks or changes in those which are currently classified as expected Adverse Drug Reactions. Any information that may affect the benefit-risk profile of apixaban will be immediately communicated to relevant Health Authorities, the DSMB, and investigators, and appropriate actions will be taken regarding the study as needed. Investigators will also be provided guidance on appropriate management of serious bleeding related events.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with this protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects in the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of any updates to the Investigator Brochure or product labeling information to be provided to subjects.

The investigator, PHN or BMS should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives or legal guardians (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS or PHN will provide the investigator with an appropriate (i.e. Global or Local) sample informed consent form (ICF) which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for the subject or the subject's legally acceptable representative or legal guardians to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative or legal guardians and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his

or her informed consent during the study, consent must additionally be obtained from the subject.

6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed Health Insurance Portability and Accountability Act (HIPAA) Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative or legal guardian must be informed of the study procedures and must sign the ICF approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This prospective, randomized, open-label, multi-center, Phase II study is designed to evaluate the safety of apixaban compared to VKA or subcutaneous LMWH, and evaluate the PK/PD of apixaban in pediatric patients. 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). To ensure even distribution of age and disease types between the two treatment groups, 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. Neonates will no longer be included in the study population [redacted].

Subjects will be randomized to receive thromboprophylaxis with open-label apixaban versus VKA or LMWH for up to 12 months or until anticoagulation is no longer needed, whichever is shorter. 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 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

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

adverse events and medication adherence. The definition of a month will be every 30 days from the date of randomization. The timing of these study visits will coincide as much as possible with the clinical care visits for these pediatric subjects. Visits will consist of clinical evaluation of thromboembolic events, bleeding events, reporting AEs, therapeutic monitoring (INR for VKA or anti-Xa activity for LMWH), monitoring medication adherence, safety laboratory studies (CBC, ALT, AST, total and conjugated bilirubin), serum or urine pregnancy test for WOCBP and concomitant therapy assessment for all enrolled subjects. Subjects on VKA or LMWH may have additional visits as needed for adjustment of their dose and monitoring at the discretion of the investigator and/or treating physician. PK/PD samples will be drawn at Day 1, Week 2, Month 3, and Month 6 only. No PK/PD sample will be drawn at the 6 month visit for subjects <3 months of age. [redacted] PK/PD [redacted] samples will be analyzed at a central core laboratory. Safety labs will be analyzed locally. See Table 5.5-1, Table 5.5-2, Table 5.5-3, and Table 5.5-4 for details of the blood sampling.

It is recommended that the subject's weight be measured at 6 weeks (only subjects < 3 months of age), 3, 6, 9, and 12 month office visits, and the apixaban dose be adjusted based on body weight changes according to the dosing guidance document that will be provided to each site.

[redacted]

QOL instruments will be administered at the Day 1, Month 6 visit, the end of study treatment (for subjects who discontinue study drug early) or Month 12 visit. If the subject is just starting an anticoagulant, the baseline KIDCLOT QOL instrument will be administered at the Week 2 visit (instead of at Day 1) (see Table above).

During the Follow-up Period, a telephone or in-person safety assessment will be scheduled at 14 Month ± 2 weeks or 2 months ± 2 weeks following cessation of study drug if duration of therapy is less than 12 months. Subjects will be instructed to report all AEs to the investigator, including those symptoms suggestive of occurrence of thrombosis or bleeding.

Early drug discontinuation: all subjects who discontinue study drug prior to the Month 12 visit should complete their end-of-study evaluation (e.g., QOL, [redacted] other laboratory tests, etc.) at the time of drug discontinuation + 2 weeks, and have a telephone or in-person safety assessment 2 months thereafter. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Definition of Last Visit: the last visit is the follow-up assessment (office visit or telephone call) at Month 14 or 2 months after study drug discontinuation.

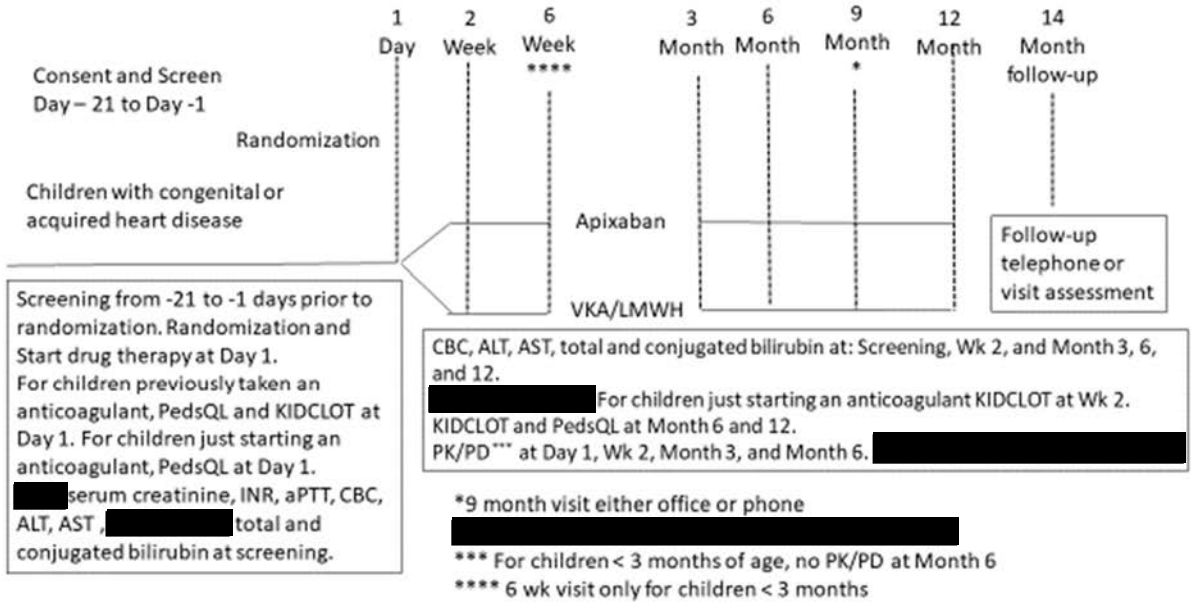
Definition of End of Study: the date of the last subject visit OR the date at which the last data point from the last subject that was required for statistical analysis (ie, key safety and efficacy results for decision making), was received, whichever is the later date.

Duration: the total duration of the trial will be approximately 4 years and includes an estimated recruitment period of 3 years and a study period up to 14 months.

[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. Enrollment was further expanded in January 2020 to subjects ages 28 days to < 3 months.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



3.2 Post-study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless it is a regulatory requirement or BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate SOC therapy to treat the condition under study.

3.3 Study Population

Subjects eligible for the study include both males and females, 28 days to < 18 years of age, weighing ≥ 3 kg, and with congenital or acquired heart disease who are at risk for clot formation that can result in vascular, intracardiac or coronary artery thrombosis, or embolization to other

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

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

b. Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days) for a total of 32 days post-treatment completion
c. It is not necessary to use any other method of contraception when complete abstinence is elected
d. Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5
e. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence
f. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

LESS EFFECTIVE METHODS OF CONTRACEPTION

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge with spermicide
4. Male or female condom with or without spermicide*
5. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

* A male and a female condom must not be used together.

UNACCEPTABLE METHODS OF CONTRACEPTION

1. Periodic abstinence (calendar, symptothermal, post-ovulation methods)
2. Withdrawal (coitus interruptus)
3. Spermicide only
4. Lactation amenorrhea method (LAM)

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Recent thromboembolic events less than 6 months prior to enrollment

b) Use of aggressive life-saving therapies such as ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) at the time of enrollment

c) Artificial heart valves or mechanical heart valves

Note: the following materials are not an exclusion: allograft/homograft valves and tissue valves; prosthetic material in the vascular system such as shunts, patches and polytetrafluoroethylene (PTFE) baffle or other prosthetic material.

2. Medical History and Concurrent Diseases

a) Known inherited bleeding disorder or coagulopathy (e.g., hemophilia, von Willebrand disease, etc.)

b) Active bleeding at the time of enrollment

c) Any major bleeding other than perioperative in the preceding 3 months

d) Uncontrolled severe hypertension (> 99th percentile of systolic or diastolic blood pressure by AAP Clinical Practice Guidelines (Appendix 2)

e) Known intracranial congenital vascular malformation or tumor

f) Confirmed diagnosis of a GI ulcer

g) Known antiphospholipid syndrome [APS])

3. Physical and Laboratory Test Findings

a) Liver dysfunction (e.g., ALT > 3X ULN and/or AST > 3X ULN and/or direct (conjugated) bilirubin > 2X ULN without an alternative causative factor such as Gilbert's syndrome, Dubin-Johnson syndrome); (subjects with a total bilirubin value ≤ 2XULN can be enrolled if the direct bilirubin values are not available)

b) Renal function < 30% of normal for age, gender, and height as determined by the Schwartz formula: (GFR [mL/min/1.73m2] = [0.413 x height (cm)] / serum creatinine (mg/dL)) (Appendix 5)

c) Platelet count < 50,000/μL

d) Weight < 3 kg

4. Allergies and Adverse Drug Reaction

a) History of allergy to apixaban or Factor Xa inhibitors

5. Reproductive Status

a) Pregnancy during the study period.

6. Other Exclusion Criteria

a) Unable to take oral or enteric medication via the NG or GT tube

b) In the opinion of the Investigator, it is not possible for the subject to be compliant with the protocol and study procedures

c) Concurrent use of another experimental drug/device or participation in another investigational drug or device trial

d) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply and Bristol-Myers Squibb approval is required)

e) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy).

3.4 Concomitant Treatments

Anticoagulant or antiplatelet use within 1 month prior to study entry must be recorded on the appropriate eCRF page. Concomitant use of non-study anticoagulant, antiplatelet, and other medications that may increase risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs [NSAIDS]) taken after randomization must be recorded on the appropriate CRF page.

3.4.1 Prohibited and/or Restricted Treatments

Once enrolled, subjects may not receive any of the following for the duration of the treatment period:

- Non-study related concurrent prophylactic or therapeutic treatment with enoxaparin, unfractionated heparin (UFH), other oral anticoagulant, or systemic thrombolytic

Note: Heparin flushes to maintain Central Venous Access Device (CVAD) patency and local tPA to restore CVAD patency are permitted. UFH and LMWH may be used as part of a bridging strategy.

- Dual anti-platelet therapy or mono anti-platelet therapy with thienopyridines such as clopidogrel, ticagrelor, or prasugrel (low dose aspirin is allowed for some conditions such as Kawasaki disease and single ventricle physiology, but aspirin doses > 5 mg/kg per day must be discussed with and approved by the medical monitor)
- Concomitant systemic treatment with strong inhibitors that inhibit both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, clarithromycin, and ritonavir (Appendix 3)

Note: Less potent CYP 3A4 and P-gp inhibitors such as fluconazole, voriconazole, topical azole antifungal agents, H2-antagonists and proton pump inhibitors are permitted.

- Concomitant systemic treatment with strong inducers of both cytochrome P450 3A4 and P-gp such as rifampin, phenytoin, and carbamazepine (Appendix 3)
- Chronic daily use of NSAIDs, (e.g., naproxen, ibuprofen, diclofenac, etc.) may increase the risk of bleeding. Therefore, concomitant use of NSAIDS for more than one consecutive month after randomization is prohibited (Appendix 4)
- During the entire study period, no other investigational agents, other than apixaban should be administered to the subjects

3.4.2 Other Restrictions and Precautions

Apixaban treatment should be discontinued at least 24 hours prior to any elective surgery or invasive procedures. Apixaban should be resumed after the procedure when adequate hemostasis has been established (e.g., after removal of surgical drains, lines, and wires, etc.), but no sooner than 24 hours after the procedure, and no later than 10 days after the procedure. Bridging strategies with UFH are permitted in the interim, per local institutional practices. Dose interruption for VKA and LMWH will follow local institutional standard practice, informed by the ACCP 2012 guideline and the local product label for TE prophylaxis.

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue the investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Use of aggressive life-saving therapies such as LVAD, or ECMO during study
- Receipt of a heart transplantation
- If a subject becomes ineligible for the study drug during the study, (e.g., receives a VAD, ECMO, or a heart transplantation), study drug must be discontinued, and treatment should be converted to the SOC per major guidelines (ACCP 2012 guideline). Perioperative use of cardiopulmonary bypass (CPB) is not an exclusion; however, apixaban treatment should be interrupted during CPB as described in section 3.4.2, and intermittent anti-coagulation (e.g., UFH) should be used per current guideline recommendations (ACCP 2012 guideline).

In the event a female subject becomes pregnant during the clinical trial, the study drug must be discontinued immediately. In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur and a decision will be made on a case-by-case basis.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the

ability to consent freely (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the CRF page.

3.6 Post Study Drug Study Follow-up

In this study, bleeding and thromboembolic events are important endpoints of the study. Post study follow-up at Month 14 (+/- 2 weeks) or 2 months after completion of anticoagulation (if the duration of anticoagulation is fewer than 12 months) is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug earlier must continue to be followed up to two months for collection of efficacy and safety outcomes and/or survival follow-up data as required and in line with Section 5.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined as the inability to reach the subject or their authorized person after a minimum of three documented phone calls, faxes, or emails as well as lack of response by the subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information. If after all attempts, the

subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy)

Apixaban, warfarin and enoxaparin will be provided by BMS as described in Table 4-1. These study drugs will be distributed from BMS to the investigational pharmacy at each site and subsequently distributed to patients per the standard procedures at each investigational pharmacy. Other VKA and LMWH can be used as per SOC, and these products will be sourced locally.

Table 4-1: Study Drugs for Treatment Period (all open label)

Product Description / Class and Dosage Form	Potency	IP/ Non-IP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Apixaban (BMS-562247-01) Capsule	0.1 mg	IP	Open Label	Bottle	Refer to the label on container
Apixaban (BMS-562247-01) Film Coated Tablet	0.5 mg	IP	Open Label	Bottles in Kit	Refer to the label on container
Apixaban (BMS-562247-01) Film Coated Tablet	5 mg	IP	Open Label	Bottle	Refer to the label on container
Apixaban (BMS-562247-01) Oral Solution	0.4 mg/mL	IP	Open Label	Bottle	Refer to the label on container
Warfarin Tablet[a]	1 mg	IP	Open Label	Bottle	Refer to the label on container
Warfarin Tablet[a]	2.5 mg	IP	Open Label	Bottle	Refer to the label on container
Warfarin Tablet[a]	5 mg	IP	Open Label	Bottle	Refer to the label on container
Enoxaparin sodium Solution for Injection[b] (US Supplies)	100 mg/mL	IP	Open Label	Multi-dose vial	Refer to the label on container
Enoxaparin sodium (Clexane) Solution for Injection[b] (ROW Supplies)	100 mg/mL	IP	Open Label	Multi-dose vial	Refer to the label on container

[a] Warfarin tablets supplied by BMS are listed in this table. If sites should choose to use another VKA according to local Standards of Care, they will be site sourced material and not supplied by BMS.

[b] Enoxaparin sodium vials supplied by BMS are listed in this table. If sites should choose to use another LMWH according to local Standards of Care, they will be site sourced material and not supplied by BMS.

Specific information regarding study drug preparation and administration will be provided to the study center by BMS.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this study, investigational product is 1) Apixaban (i.e. BMS-562247) in capsules, tablets, and oral solution, 2) warfarin in tablets or other VKA, and 3) LMWH in solution. Apixaban, warfarin, and enoxaparin will be provided by BMS as described in Table 4-1. Other site selected VKA and LMWH will be sourced locally.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

4.3 Storage of Study Drug

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS should be contacted.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Please refer to Section 9.2.2 for guidance on IP records and documentation.

4.4 Method of Assigning Subject Identification

At enrollment, each subject will be assigned a unique sequential number by the IWRS. The IWRS will be available 24 hours per day, seven days a week. The subject number will consist of a unique 5 digit number that is assigned sequentially within a study (starting with 00001) by the IWRS. This number will be used for identification throughout the study and will not be used for any other subject.

Subjects will be randomized to apixaban or active comparator (VKA or LMWH) in a 2:1 ratio by the IWRS. Randomization schedules will be generated and kept by BMS. Randomization will be stratified by age groups as well as single ventricle congenital heart disease vs other congenital and acquired heart disease to ensure even distribution between the two treatment groups.

4.5 Selection and Timing of Dose for Each Subject

[redacted] Recruitment started first 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 in February 2020.

Apixaban will be administered in accordance with the dosing instructions provided in separate documents and in Table 4-1. For subjects who are currently on the mg/kg dosing regimen, their dosing will be switched to the fixed-dose, body weight-tiered regimen at their next scheduled visit.

Table 4.5-1: Apixaban Doses for Ages 28 Days to < 18 Years

Weight range	Dose	Apixaban Formulation*
3 to < 4 kg	0.2 mg twice daily	0.1 mg capsules
4 to < 5 kg	0.3 mg twice daily	0.1 mg capsules
5 to < 6 kg	0.5 mg twice daily	0.5 mg tablets
6 to < 9 kg	1 mg twice daily	0.5 mg tablets
9 to < 12 kg	1.5 mg twice daily	0.5 mg tablets
12 to < 18 kg	2 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
18 to < 25 kg	3 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
25 to < 35 kg	4 mg twice daily	0.5 mg tablets or 0.4 mg/ml oral solution
≥35 kg	5 mg twice daily	5 mg tablet or 0.4 mg/ml oral solution

*For children < 5 years available formulations include 0.1 mg capsule or 0.5-mg tablets

For children < 5 years the 0.4 mg/ml oral formulation cannot be used

For children ≥ 5 years, available formulations include 0.5-mg tablets, 5 mg tablets (use only if body weight ≥ 35 kg), or 0.4 mg/ml oral solution

Children aged 28 days to < 18 years of age are eligible for the study. Children randomized to the apixaban arm of the study weighing between 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2 mg and 4 mg depending on body weight with the 0.1 capsules, 0.5 mg mini-tablets, or oral solution. Instructions will be provided on how to dissolve the 0.1 mg capsules and suspend the mini-tablets into solution. Alternatively, children ≥ 5 years will have the option of using the oral solution formulation at the same doses as would be recommended for the 0.1 mg capsule or mini-tablet formulation. Note that children < 5 years of age will not have the option of being dosed via the oral solution formulation.

Children randomized to the apixaban arm of the study weighing ≥ 35 kg will be administered apixaban 5 mg twice daily (BID) as a tablet or solution.

Apixaban doses can be administered by mouth (PO) or via a NGT or GT approximately 12 hours apart, followed with or without food. The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor. The apixaban 5 mg tablet can be crushed and suspended in water or 5% dextrose in water (D5W) or apple juice or can be mixed with applesauce and promptly administered orally. Alternatively, apixaban 5 mg tablets can be crushed and suspended in 60 mL of water or D5W and promptly delivered through a NGT. The apixaban 0.5 mg tablets can be mixed with applesauce or can be dissolved in water, apple juice, or formula and promptly administered orally or via NGT/GT. Apixaban should not be administered through NJT/post-pyloric feeding tubes due to decreased absorption. The apixaban 0.1 mg capsules will need to be opened and dissolved in infant formula or breast milk and promptly administered orally or via NGT/GT.

The subject's weight will be measured at the 6 week (subjects < 3 months only), 3, 6, 9 (subjects < 2 years only), and 12 month office visits, and the apixaban dose should be adjusted based on body weight changes according to the dosing guidance document that will be provided separately. Apixaban can be administered by mouth (PO) or via a NGT or G-tube, beginning when subjects are able to tolerate enteral intake. Subjects 28 days to < 3 months must be able to tolerate oral/NGT/GT feeds for at least 5 days prior to randomization.

Apixaban should not be administered through NJT/post-pyloric feeding tubes due to decreased absorption. For post-operative subjects, study medication should begin when subjects are able to tolerate enteral intake after the procedure when adequate hemostasis has been established (e.g., after removal of surgical drains, lines, and wires, etc.), but no sooner than 24 hours after the procedure and no more than 10 days after surgery. Chest tubes and other instrumentation that could cause bleeding should be removed prior to initiation of therapy. Bridging strategies with UFH are permitted in the interim, per local institutional practices. The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor.

It is recommended that subjects take their study medication at the same time each day.

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL. Exact targets may vary by condition and local standard of care. All INR (for subjects taking VKA) and anti-Xa (for subjects taking LMWH) values obtained during the study period per SOC will be recorded at each study visit. Patient diaries will be used to record study drug administration.

4.5.1 Missed Dose and Vomiting/Regurgitation

If a dose of apixaban is missed the subject should take the study medication immediately and then continue with twice daily administration as before. A double dose should not be taken to make up for a missed dose. Subjects may take a missed dose up to 6 hours after the normal dosing time. If it is greater than 6 hours from the normal dosing time, the missed dose should not be taken. Instead, the next scheduled dose should be taken at its normal time.

If a subject vomits or regurgitates within 30 minutes after ingestion of the study drug, re-dosing is allowed; but the study drug can be given again one time only. If the subject vomits/regurgitates more than 30 minutes after study drug ingestion, no additional study drug should be taken, and the subject should resume study drug ingestion according to the usual schedule.

4.5.2 Temporary Treatment Interruptions

During the course of the study, situations might occur in which the investigator considers a temporary interruption of study drug treatment necessary. For example, a scheduled surgical procedure, perioperative use of CPB, or elevated liver function tests. The treating physician should be informed about recommendations for timing and dosage of study drug (apixaban or active comparator) administration in such circumstances.

For treatment interruptions ≥ 48 consecutive hours, the period of interruption should be noted and the investigator should document on the CRF the time and date of discontinuation and restart of therapy, as well as the reason for interruption and measures taken to correct the event. An AE should be reported if applicable.

Guidance on temporary dose interruptions for selected events are described below. For an individual subject, dose interruptions and treatment discontinuation may be more or less conservative than indicated below based on the clinical judgment of the investigator. Note that discontinuation of subjects from treatment is addressed in Section 3.5.

Elective Procedure or Surgery

Apixaban: The effective half-life of apixaban when administered twice daily is approximately 12 hours, and it is expected that most of the anticoagulation effect will be gone within 24 hours after the last dose of the drug. Apixaban must be stopped for a sufficient period of time (e.g., at least 24 hours if the risk of bleeding is low and at least 48 hours if the risk of bleeding is moderate or high) prior to the procedure to minimize the risk of anticoagulant-related bleeding. The treating physician should be made aware of the time and dosage of apixaban administration and be informed that routine coagulation tests such as INR and aPTT are relatively insensitive measures of anticoagulation activity and are unsuitable for monitoring the anticoagulation effect of apixaban. The subject will re-start study medication once hemostasis is secure (e.g., after removal of surgical drains, lines, and wires, etc.), and when, in the opinion of the investigator, it is safe to do so, at such time as a patient would otherwise be transitioned to VKA or LMWH per local institutional standards, but no earlier than 24 hours and no later than 10 days after the procedure/surgery. Bridging strategies with UFH are permitted in the interim, per local institutional practices.

Elevated Liver Function Tests (applies to both the apixaban and comparator groups)

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:

1) ALT/AST < 5 x ULN and direct (conjugated) bilirubin ≤ 2 x ULN, study medication may continue.
2) 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

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

OR

- Direct (conjugated) bilirubin > 2 x ULN on any two consecutive occasions.

All subjects with an ALT/AST ≥ 5 x ULN or direct (conjugated) bilirubin > 2 x ULN will be followed weekly until ALT/AST returns to < 3 x ULN or to baseline, and direct (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 BMS Medical Monitor and perform the following:

- INR, 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.

4.5.3 Converting from or to Apixaban

Switching from VKA to apixaban: VKA should be discontinued and apixaban started when the INR is below 2.0.

Switching from apixaban to VKA: apixaban may affect INR, so that INR measurements during co-administration with VKA may not be useful for determining the appropriate dose of VKA. If continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant and VKA at the time the next dose of apixaban would have been taken, discontinuing the parenteral anticoagulant when the INR reaches an acceptable range per institutional standards.

Switching between apixaban and anticoagulants other than VKA: discontinue one being taken and begin the other at the next scheduled dose.

4.6 Blinding/Unblinding

Not applicable, this is an open label study.

4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced.

For inpatients, apixaban will be administered in the clinical facility under the supervision of clinical staff. The date and volume or dosage of administered drug will be recorded at the clinical site by clinical or research personnel in the subject's diary and eCRF. If an infant or a young child regurgitates a portion of or the entire drug product during or after administration, this should be recorded in the eCRF.

At each study visit, the subject/parents should bring the study medication and compliance will be assessed based upon subject's/parents interview and a count of the tablets or volume of solution returned. Compliance should be between ≥ 80% and ≤ 120% of that prescribed, excluding any protocol defined dose interruption period. The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the CRF. If a subject is not ≥ 80% compliant after exclusion of the protocol defined dose interruption period, then the period of non-compliance should be noted as a protocol deviation and the sponsor should be notified. The subject should be re-educated regarding medication compliance.

4.8 Destruction or Return of Investigational Product

For this study, IP (those supplied by BMS, a vendor, or sourced by the investigator) such as partially used study drug containers may be destroyed on site.

If...	Then...
IP supplied by BMS (including its vendors)	Any unused IP supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless IP containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). If IP will be returned, the return will be arranged by the responsible Study Monitor.
IP sourced by site, not supplied by BMS (or its vendors) (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e. incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of IP provided by BMS (or its vendors). Destruction of non-IP sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

Please refer to Section 9.2.2 for additional guidance on IP records and documentation.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CV185362)

Procedure	Consent/ Screening Visit Day -21 to 1	Randomization Visit Day 1	Notes
Eligibility Assessments			
Informed Consent	X		Informed consent must be signed prior to initiating any study procedures
Inclusion/Exclusion Criteria	X	X	Includes assessment of the indication for thromboprophylaxis
Medical History	X		Includes collection of disease specific medical and surgical history and primary diagnosis
Physical Measurements	Height, Body Weight, and calculated Body Mass Index	Body Weight	Body weight must be ≥ 3 kg
Concomitant Medication Assessment	X	X	Medications taken 1 month prior to enrollment, at the time of signing the informed consent and after signing the informed consent must be recorded on the appropriate CRF page
Safety Assessments			
Full Physical Examination	X		Includes assessment of signs of thromboembolism or bleeding
Vital Signs	X		Heart Rate, BP, respiratory rate and temperature
Assessment of Signs and Symptoms		X	Signs and symptoms of thromboembolism or bleeding
Serious Adverse Events Assessment	X	X	Collection of SAEs begins after signed consent
Adverse Events Assessment		X	Collection of non-serious AEs begins after randomization

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

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

Table 5.1-1: Screening Procedural Outline (CV185362)

Procedure	Consent/ Screening Visit Day -21 to 1	Randomization Visit Day 1	Notes
			LMWH will be sourced locally by the study site. Study drug diaries will be used to record study drug administration.
Dispense Patient Diary		X	Patient diary will be used to collect dose, date, and time of when study medication is administered to the subject

[redacted]

Table 5.1-2: Study Procedural Outline (CV185362)

Procedure	During Treatment[d]					End of Treatment	Follow-up	Notes
	Week 2 ± 3 days	Week 6 ±3days (only subjects < 3 months at time of randomization)	Month 3 ± 2 weeks	Month 6 ± 2 weeks [e]	Month 9 ± 2 weeks	Month 12 ± 2 weeks or early drug discontinuation	Month 14 ± 2 weeks (or 2 months after the end of anticoagulation)	
Concomitant Medication Assessment	X		X	X	X	X	X	Subjects ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. Subjects < 2 years of age are required to have an office visit
Body Weight		X	X	X	X	X		Apixaban dose should be adjusted based on body weight changes according to dosing guidance document provided to the site. Subjects ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. Body weight will only be taken at the office visits
Safety Assessments								
Targeted Physical Examination	X		X	X		X		Includes organ systems pertinent to the subject's signs, symptoms, or adverse events, e.g., assessment of signs of bleeding
Vital Signs	X		X	X		X		Heart Rate, BP, respiratory rate and temperature
Serious Adverse Event Assessment	X	X	X	X	X	X	X	Collection of SAEs begins after signed consent. Subjects ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. The 6 week visit is only for those subjects < 3 months.
Adverse Events Assessment	X	X	X	X	X	X	X	Collection of non-serious AEs begins after randomization. Subjects ≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks. The 6 week

Table 5.1-2: Study Procedural Outline (CV185362)

Procedure	During Treatment[d]					End of Treatment	Follow-up	Notes
	Week 2 ± 3 days	Week 6 ±3days (only subjects < 3 months at time of randomization)	Month 3 ± 2 weeks	Month 6 ± 2 weeks [e]	Month 9 ± 2 weeks	Month 12 ± 2 weeks or early drug discontinuation	Month 14 ± 2 weeks (or 2 months after the end of anticoagulation)	
								visit is only for those subjects < 3 months.
Laboratory Tests[a]	X		X	X		X		CBC, ALT, AST, total and conjugated bilirubin for all subjects. INR for subjects receiving VKA or anti-Xa activity for subjects receiving LMWH as per SOC
Pregnancy Test WOCBP only	X		X	X		X		
[redacted]								
PK, PD [redacted]								
PK Sampling Apixaban patients only[b]	X		X	X				Week 2: Pre-dose sample Month 3: 2 ± 1 hr post dose sample Month 6: Pre-dose sample For those children < 3 months of age at randomization, blood samples will only be taken at Day 1, Week 2, and Month 3. A dried blood spot technique can be used for PK sampling in children < 3 months of age at randomization
Anti-Xa Sampling Apixaban	X		X	X				Week 2: Pre-dose sample

Table 5.1-2: Study Procedural Outline (CV185362)

Procedure	During Treatment[d]					End of Treatment	Follow-up	Notes
	Week 2 ± 3 days	Week 6 ±3days (only subjects < 3 months at time of randomization)	Month 3 ± 2 weeks	Month 6 ± 2 weeks [e]	Month 9 ± 2 weeks	Month 12 ± 2 weeks or early drug discontinuation	Month 14 ± 2 weeks (or 2 months after the end of anticoagulation)	
patients only[b]								Month 3: 2 ± 1 hr post dose sample Month 6: Pre-dose sample For those children < 3 months of age at randomization, blood samples will only be taken at Month 3.
Chromogenic FX Assay Sampling Apixaban patients only[b]			X	X				Month 3: 2 ± 1 hr post dose sample Month 6: Pre-dose sample For those children < 3 months of age at randomization, blood samples will only be taken at Day 1 and Month 3.
[redacted]								
Efficacy Assessments								
QOL assessment	X			X		X		If the subject is just starting an anticoagulant, KIDCLOT only to be completed by English speaking subjects at Week 2 visit. The QOL will be completed for all subjects at the Month 6 visit, and the end of study treatment (for subjects who discontinue study drug early) or Month 12 visit. The QOL needs to be completed at the time of the visit
Thromboembolic events	X		X	X	X	X	X	Record thromboembolic events in the appropriate CRF page; send pertinent documents for adjudication. Subjects

Table 5.1-2: Study Procedural Outline (CV185362)

Procedure	During Treatment[d]					End of Treatment	Follow-up	Notes
	Week 2 ± 3 days	Week 6 ±3days (only subjects < 3 months at time of randomization)	Month 3 ± 2 weeks	Month 6 ± 2 weeks [e]	Month 9 ± 2 weeks	Month 12 ± 2 weeks or early drug discontinuation	Month 14 ± 2 weeks (or 2 months after the end of anticoagulation)	
								≥ 2 years of age have the option of an in-person or a phone call visit at 9 months ± 2 weeks
Study Drug								
Dispense Study Drug		X*	X	X	X*			*For subjects who will have a Week 6 or Month 9 office visit, study medication will be dispensed. Dose will be adjusted for weight gain if necessary. Study drug diaries will be used to record study drug administration
Collect Patient Diary			X	X	X	X		If subject is there for an office visit, verify patient diary completion, study drug compliance, and dispense patient diary back to subject
End taking Study Drug						X		The study medication will start on Day 1 and continue up to 12 months or until the need for anticoagulant is resolved, whichever is shorter.

[a] INR levels for subjects receiving VKA and anti-Xa levels for subjects receiving LMWH as part of SOC will also be collected between visits per SOC and recorded at each visit. Those INRs collected between visits via a home monitoring device will be logged in diaries and recorded at the subsequent visit.

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

[redacted]

d Week 6 visit only for those subjects < 3 months of age at the time of randomization

e No PK/FXa/chromogenic samples taken at Month 6 for children < 3 months

5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e. the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-2, Screening Procedural Outline may be repeated during the Screening period in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

BMS will supply the sites with the following materials:

- Electronic CRFs
- BMS SAE electronic CRF Form
- BMS Pregnancy Surveillance Form
- Adjudication binder and worksheets
- Mandatory Subject diary for study medication. The date of doses should be completed daily by the subject/ parent or study staff
- Laboratory manuals
- Study Reference materials

5.3 Safety Assessments

Safety Assessments will include AE reporting as well as bleeding events assessment.

The procedures described in the sections below will be completed to ensure subject's safety.

5.3.1 Bleeding Assessment

Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) criteria,[29] and are described as follows:

Major bleeding is defined as bleeding that satisfies one or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/dL) in a 24 hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (iv) bleeding that requires surgical intervention in an operating suite (including interventional radiology).

Clinically relevant non-major (CRNM) bleeding is defined as bleeding that satisfies one or both of the following: (i) overt bleeding for which a blood product is administered and which is

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

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

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]

[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.

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]

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).

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).

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.

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.

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,

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

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

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.

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 8.1-1: 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.

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.

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]

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.

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.

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.

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.

9.2.2 Study Drug Records

Records for IP (whether supplied by BMS, its vendors, or the site) must substantiate IP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	• Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture (EDC) tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS EDC tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS EDC tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (e.g., among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (e.g., among top quartile of enrollers from a specified region or country)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA). These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An AE that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	SAE defined as 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; results in persistent or significant disability/incapacity, is 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADME	absorption/distribution/metabolism/execretion
AE	adverse event
[redacted]	
ALT	alanine aminotransferase
[redacted]	
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	
AUC	area under the concentration-time curve
[redacted]	
AUC(TAU)	area under the concentration-time curve in one dosing interval
[redacted]	
BID, bid	bis in die, twice daily
[redacted]	
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
[redacted]	
C	Celsius
[redacted]	
CBC	complete blood count
[redacted]	

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

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

Term	Definition
[redacted]	
L	liter
LAM	Lactation amenorrhea method
LC	liquid chromatography
[redacted]	
mg	milligram
min	minute
mL	milliliter
[redacted]	
µg	microgram
N	number of subjects or observations
N/A	not applicable
ng	nanogram
NGT	nasogastric
[redacted]	
NOACs	novel oral anticoagulants
NSAID	nonsteroidal anti-inflammatory drug
NVAF	non-valvular atrial fibrillation
[redacted]	
PD	pharmacodynamics
PE	pulmonary embolism
PHN	Pediatric Heart Network
PK	pharmacokinetics
PO	per os (by mouth route of administration)
[redacted]	
QC	quality control
QD, qd	quaque die, once daily
QOL	quality of life
RBC	red blood cell
[redacted]	

Term	Definition
SAE	serious adverse event
SD	standard deviation
SOC	standard of care
SOP	Standard Operating Procedures
t	temperature
T	time
[redacted]	
TE	thromboembolism
[redacted]	
UFH	unfractionated heparin
ULN	upper limit of normal
US	United States
[redacted]	
VAD	ventricular assist devices
VKAs	vitamin K antagonists
[redacted]	
VTE	venous thromboembolism
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
[redacted]	
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
[redacted]	

12 REFERENCES

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APPENDIX 1 BLOOD SAMPLING

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
Safety Labs: CBC AST/ALT T/D bilirubin INR[c], aPTT[c] Serum creatinine[c] Pregnancy[d]	All Subjects	X		X	X	X	X	~3-5 ml / sample
Serial PK and anti-FXa activity[b]	Subjects taking Apixaban		4 hr (3-8 hr)	Predose	2 ± 1 hr Post dose	Predose		1.4 mL sample children < 1 year of age 2 ml sample children ≥ 1 year of age sample for PK and anti-FXa combined
Chromogenic FX[b]	Subjects taking Apixaban		Prior to first dose,[e] and 4 hr (3-8 hr)[a]		2 ± 1 hr Post dose	Predose		1.4 ml / sample
[redacted]								

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]

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.

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

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.

APPENDIX 2 BLOOD PRESSURE (BP) LEVELS FOR BOYS AND GIRLS BY AGE AND HEIGHT PERCENTILE[1]

Instructions for using this BP Chart:

1) Measure the patient's blood pressure using an appropriate size cuff
2) Select appropriate chart for a female or male patient
3) Using the "age" row and "height" column determine if the BP is < 99%

Table 4 BP Levels for Boys by Age and Height Percentile

TABLE 4 BP Levels for Boys by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	30.4	30.8	31.6	32.4	33.3	34.1	34.6	30.4	30.8	31.6	32.4	33.3	34.1	34.6
	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	50th	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	90th	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	95th	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	95th + 12 mm Hg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (in)	33.9	34.4	35.3	36.3	37.3	38.2	38.8	33.9	34.4	35.3	36.3	37.3	38.2	38.8
	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	50th	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	90th	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mm Hg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (in)	36.4	37	37.9	39	40.1	41.1	41.7	36.4	37	37.9	39	40.1	41.1	41.7
	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	50th	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	90th	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mm Hg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (in)	38.8	39.4	40.5	41.7	42.9	43.9	44.5	38.8	39.4	40.5	41.7	42.9	43.9	44.5
	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	50th	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	90th	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mm Hg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (in)	41.1	41.8	43.0	44.3	45.5	46.7	47.4	41.1	41.8	43.0	44.3	45.5	46.7	47.4
	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	50th	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	90th	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (in)	43.4	44.2	45.4	46.8	48.2	49.4	50.2	43.4	44.2	45.4	46.8	48.2	49.4	50.2
	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	50th	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	90th	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mm Hg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (in)	45.7	46.5	47.8	49.3	50.8	52.1	52.9	45.7	46.5	47.8	49.3	50.8	52.1	52.9
	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	50th	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	90th	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mm Hg	122	122	123	124	126	127	128	83	83	84	85	85	86	86

TABLE 4 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.8	48.6	50	51.6	53.2	54.6	55.5	47.8	48.6	50	51.6	53.2	54.6	55.5
	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	50th	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	90th	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mm Hg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (in)	49.6	50.5	52	53.7	55.4	56.9	57.9	49.6	50.5	52	53.7	55.4	56.9	57.9
	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	50th	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	90th	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mm Hg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (in)	51.3	52.2	53.8	55.6	57.4	59.1	60.1	51.3	52.2	53.8	55.6	57.4	59.1	60.1
	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	50th	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	90th	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mm Hg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (in)	53	54	55.7	57.6	59.6	61.3	62.4	53	54	55.7	57.6	59.6	61.3	62.4
	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	50th	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	90th	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mm Hg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (in)	55.2	56.3	58.1	60.1	62.2	64	65.2	55.2	56.3	58.1	60.1	62.2	64	65.2
	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	50th	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	90th	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mm Hg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (in)	57.9	59.1	61	63.1	65.2	67.1	68.3	57.9	59.1	61	63.1	65.2	67.1	68.3
	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	50th	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	90th	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	95th	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	95th + 12 mm Hg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height (in)	60.6	61.8	63.8	65.9	68.0	69.8	70.9	60.6	61.8	63.8	65.9	68.0	69.8	70.9
	Height (cm)	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	50th	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	90th	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	95th	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	95th + 12 mm Hg	135	137	139	142	144	145	146	89	90	91	93	94	95	96

TABLE 4 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	62.6	63.8	65.7	67.8	69.8	71.5	72.5	62.6	63.8	65.7	67.8	69.8	71.5	72.5
	Height (cm)	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	50th	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	90th	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	95th	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	95th + 12 mm Hg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height (in)	63.8	64.9	66.8	68.8	70.7	72.4	73.4	63.8	64.9	66.8	68.8	70.7	72.4	73.4
	Height (cm)	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	50th	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	90th	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	95th	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	95th + 12 mm Hg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height (in)	64.5	65.5	67.3	69.2	71.1	72.8	73.8	64.5	65.5	67.3	69.2	71.1	72.8	73.8
	Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	50th	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	90th	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	95th	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	95th + 12 mm Hg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

Table 5 BP Levels for Girls by Age and Height Percentile

TABLE 5 BP Levels for Girls by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	90th	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	95th	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	95th + 12 mm Hg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (in)	33.4	34	34.9	35.9	36.9	37.8	38.4	33.4	34	34.9	35.9	36.9	37.8	38.4
	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	50th	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	90th	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mm Hg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (in)	35.8	36.4	37.3	38.4	39.6	40.6	41.2	35.8	36.4	37.3	38.4	39.6	40.6	41.2
	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	50th	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	90th	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mm Hg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (in)	38.3	38.9	39.9	41.1	42.4	43.5	44.2	38.3	38.9	39.9	41.1	42.4	43.5	44.2
	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	50th	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	90th	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (in)	40.8	41.5	42.6	43.9	45.2	46.5	47.3	40.8	41.5	42.6	43.9	45.2	46.5	47.3
	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	50th	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	90th	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mm Hg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (in)	43.3	44	45.2	46.6	48.1	49.4	50.3	43.3	44	45.2	46.6	48.1	49.4	50.3
	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	50th	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	90th	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mm Hg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (in)	45.6	46.4	47.7	49.2	50.7	52.1	53	45.6	46.4	47.7	49.2	50.7	52.1	53
	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	50th	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	90th	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mm Hg	121	122	123	124	125	126	127	84	84	85	85	86	86	87

TABLE 5 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
15	Height (in)	59.7	60.6	62.2	63.9	65.6	67.2	68.1	59.7	60.6	62.2	63.9	65.6	67.2	68.1
	Height (cm)	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	50th	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	90th	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	95th	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	136	137	138	139	139	140	92	92	92	93	94	94	94
16	Height (in)	59.9	60.8	62.4	64.1	65.8	67.3	68.3	59.9	60.8	62.4	64.1	65.8	67.3	68.3
	Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	50th	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	90th	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	95th	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height (in)	60.0	60.9	62.5	64.2	65.9	67.4	68.4	60.0	60.9	62.5	64.2	65.9	67.4	68.4
	Height (cm)	152.4	154.7	158.7	163.0	167.4	171.3	173.7	152.4	154.7	158.7	163.0	167.4	171.3	173.7
	50th	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	90th	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	95th	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	95th + 12 mm Hg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

Use percentile values to stage BP readings according to the scheme in Table 3 (elevated BP: ≥90th percentile; stage 1 HTN: ≥95th percentile; and stage 2 HTN: ≥95th percentile + 12 mm Hg). The 50th, 90th, and 95th percentiles were derived by using quantile regression on the basis of normal-weight children (BMI <85th percentile).[77]

TABLE 5 Continued

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
		Height Percentile or Measured Height							Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
8	Height (in)	47.6	48.4	49.8	51.4	53	54.5	55.5	47.6	48.4	49.8	51.4	53	54.5	55.5
	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	50th	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	90th	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mm Hg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (in)	49.3	50.2	51.7	53.4	55.1	56.7	57.7	49.3	50.2	51.7	53.4	55.1	56.7	57.7
	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	50th	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	90th	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mm Hg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (in)	51.1	52	53.7	55.5	57.4	59.1	60.2	51.1	52	53.7	55.5	57.4	59.1	60.2
	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	50th	96	97	98	99	101	102	103	58	59	59	60	61	61	62
	90th	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mm Hg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (in)	53.4	54.5	56.2	58.2	60.2	61.9	63	53.4	54.5	56.2	58.2	60.2	61.9	63
	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	50th	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	90th	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mm Hg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (in)	56.2	57.3	59	60.9	62.8	64.5	65.5	56.2	57.3	59	60.9	62.8	64.5	65.5
	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	50th	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	90th	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mm Hg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (in)	58.3	59.3	60.9	62.7	64.5	66.1	67	58.3	59.3	60.9	62.7	64.5	66.1	67
	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	50th	104	105	106	107	108	108	109	62	62	63	64	65	65	66
	90th	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	95th	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	95th + 12 mm Hg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height (in)	59.3	60.2	61.8	63.5	65.2	66.8	67.7	59.3	60.2	61.8	63.5	65.2	66.8	67.7
	Height (cm)	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	50th	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	90th	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	95th	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	95th + 12 mm Hg	135	135	136	137	138	139	139	92	92	92	92	93	93	94

APPENDIX 3 COMMON STRONG INHIBITORS OF BOTH CYTOCHROME P450 3A4 (CYP3A4) AND P-GLYCOPROTEIN (P-GP) (NOT ALL INCLUSIVE)[2]

Apixaban is hepatically metabolized by cytochrome P-450 3A4 (CYP3A4) and is a substrate for the efflux transporter P-glycoprotein (P-GP). Co-administration of drugs that are strong inhibitors of both CYP3A4 and P-GP can increase apixaban blood concentrations. Patients with renal insufficiency or of low body weight may be at increased risk of excessive anticoagulation due to CYP and P-gp drug interactions, and avoidance of certain drug combinations should be considered.

Examples of strong inhibitors of CYP3A4 are prohibited while subjects are on treatment with BMS-562247. Some examples of strong inhibitors of CYP3A4 are:

Clarithromycin	nelfinavir
telithromycin	ritonavir
itraconazole	saquinavir
ketoconazole	indinavir
voriconazole	cobicistat
posaconazole	

Strong inducers of P-gp and CYP3A4 are expected to decrease apixaban blood concentrations and can result in failure of therapeutic anticoagulant effect.

Examples of strong inducers of both CYP3A4 and P-gp are:

Rifampin	phenytoin
carbamazepine	St. John's wort

These lists are not meant to be all inclusive. Please consult individual drug labels for further information.

Management suggestions:

Avoid co-administration of strong inhibitors of both CYP3A4 and P-gp. Bleeding risk is expected to be further increased in patients with renal insufficiency, depending upon severity.

The efficacy of routine coagulation testing to evaluate the degree of anticoagulation with apixaban is limited.

Avoid co-administration of strong inducers of both CYP34 and P-gp.

APPENDIX 4 COMMON NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (NOT ALL INCLUSIVE)

Over-the-Counter NSAIDS

BRAND NAME	GENERIC NAME
Advil, Motrin	ibuprofen
Aleve	naproxen sodium
Ascriptin, Bayer, Ecotrin	aspirin

Prescription NSAIDS

BRAND NAME	GENERIC NAME
Anaprox	naproxen sodium
Celebrex	celecoxib
Clinoril	sulindac
Daypro	oxaprozin
Disalcid	salsalate
Dolobid	diflunisal
Feldene	piroxicam
Indocin	indomethacin
Lodine	etodolac
Mobic	meloxicam
Naprosyn	naproxen
Relafen	nabumetone
Toradol	ketorolac tromethamine
Vimovo	naproxen/esomeprazole
Voltaren	diclofenac

APPENDIX 5 GFR ASSESSMENT

Inadequate renal function is defined as <30% of 1 standard deviation (SD) below normal GFR for age, gender, and height as determined by the Schwartz formula [eGFR (ml/min/1.73m2) = 0.413 * (height (cms)/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.

Table 4: GFR Assessment

Age (sex)	Normal GFR (Mean GFR ± SD) (mL/min/1.73m2)	GFR for study qualification[a] (Mean GFR) (mL/min/1.73m2)
1 week (males and females)	41 ± 15	≥ 8
2 - 8 weeks (males and females)	66 ± 25	≥ 12
> 8 weeks to < 2 years (males and females)	96 ± 22	≥ 22
2 - 12 years (males and females)	133 ± 27	≥ 30
13 - 17 years (males)	140 ± 30	≥ 30
13 - 17 years (females)	126 ± 22	≥ 30

a Patient may be enrolled if GFR is at or greater than this value as determined by Schwartz formula

APPENDIX 6 REFERENCES FOR APPENDICES

1 NHBPEP: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004;114;555-576

2 Modified from Uptodate: www.uptodate.com. Accessed: November 11, 2013. Anticoagulation with direct thrombin inhibitors and factor Xa inhibitors. Table 3: Apixaban pharmacokinetic interactions.

3 Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New Equations to Estimate GFR in Children with CKD. JASN 2009; 20: 629-637.

APPENDIX 7 REVISED PROTOCOL SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 03, dated 27-Jan-2020:

The main reason for revising the protocol is 1) to open enrollment to patients 28 days to < 3 months and 2) introduce the 0.1 mg apixaban capsule for patients 3 kg to < 6 kg

The revised protocol applies to all future participants and to all participants currently enrolled.

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis; Investigational Product	Open enrollment to patients aged 28 days to < 3 months	Open enrollment to all the ages specified in the protocol
Synopsis; Investigational Product	Introduce 0.1 mg apixaban capsules	0.1 mg capsules needed to allow apixaban dosing to children < 3 months of age
Synopsis; Study Design Schematic	Add a 6 week visit to those patients < 3 months of age	6 week visit needed to weigh patients in order to adjust apixaban dose
Synopsis; Inclusion Criteria	Indicate that subjects aged 28 days to < 3 months must be able to tolerated oral/NGT/GT feeds for at least 5 days	Define an eligible patient
Synopsis; Exclusion Criteria	Update exclusion criteria to 'known inherited bleeding disorder or coagulopathy (eg, hemophilia, von Willebrand disease, etc' and 'known antiphospholipid syndrome'	Provide additional safety precautions and refine broad exclusion criteria
Synopsis; Study Assessments; PK	Add the use of dried blood spot collection method for PK sampling for patients < 3 months	Conserve blood volume used for study samples in young infants
[redacted]		
Synopsis; Table; Apixaban Dose table	Add apixaban doses for weight range tiers between 3 and < 6 kg	Allow apixaban doses for weights between 3 and < 6 kg
Synopsis; Table 1-1 Sampling schedule for PK, PD [redacted] for children ≥ 1 to < 18 years of age	Replace 1.0 ml blood collection tube with a 1.4 ml tube thereby increasing the total blood volume by 1.6 ml	Sourcing issues require replacing 1.0 ml tube with a 1.4 ml tube
Synopsis; Table 1.2 and Table 1.3 Sampling Schedule	Add sampling schedule for children aged 3 months to < 1 year and ages 28 days to < 3 months	Provide clarity on the sampling schedule for all ages
Body; Section 1.1-1; Rationale for Dose	Provide reason why weight tiered dosing scheme was implemented	Allow a solid dose formulation to be used
Body; Section 1.1-1; Rationale for Dose	Expand enrollment to children down to 28 days	To allow all ages specified by the protocol to be included
Body; Section 1.1-1; Rationale	Introduce the 0.1 mg apixaban capsule	To allow axixaban dosing for

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
for Dose		those children < 3 months of age
Body; Section 1.1.2; Rationale for Dose	Add mixing instructions for the use of the 0.1 mg apixaban capsule	Mixing instructions for apixaban formulation
Body; Section 1.4 Product Development Background	Describe palatability and bioavailability testing of the 0.1 mg apixaban capsules	Testing to support the use of the 0.1 mg apixaban formulation
Body; Section 1.4 Product Development Background; Update on Apixaban Pediatric Formulation	Describe the 0.1 mg apixaban capsule	Provide information on the apixaban formulation
Body; Section 1.4 Product Development Background; Apixaban Dose Selection	Introduce expanding enrollment down to 28 days and the use of the 0.1 mg apixaban capsule	Allow enrollment of children 28 days to < 3 months of age
Body; Section 1.4 Product Development Background; Apixaban Dose Selection; Table 1.4.1	Increase weight range table to include weight tiers of 3 to < 4 kg, 4 kg to < 5 kg, 5 kg to < 6 kg	Describe the additional weight tiers for apixaban dosing
Body; Section 3.1 Study Design and Duration	Add the use of dried blood spot collection method for PK sampling for patients < 3 months	Conserve blood volume used for study samples in young infants
[redacted]		
Body; Section 3.1 Study Design and Duration	Add a 6 week visit to those patients < 3 months of age	6 week visit needed to weigh patients in order to adjust apixaban dose
Body; Section 3.1 Study Design and Duration; Figure 3.1.1 Study Design Schematic	Add a 6 week visit to those patients < 3 months of age	6 week visit needed to weigh patients in order to adjust apixaban dose
Body; Section 3.3.1 Inclusion Criteria; Target Population	Indicate that subjects aged 28 days to < 3 months must be able to tolerated oral/NGT/GT feeds for at least 5 days	Define an eligible patient
Body; Section 3.3.1 Inclusion Criteria; Age and Reproductive Status	Change inclusion age from 34 weeks to < 18 years to 37 weeks to < 18 years	Adjust enrollment ages
Body; Section 4 Study Drug; Table 4.1 Study drugs	Add 0.1 mg apixaban capsule	Describe all the apixaban formulations
Body; Section 4.5 Selection and Timing of Dose	Expand enrollment down to 28 days	Adjust enrollment ages
Body; Section 4.5 Selection and Timing of Dose; Table 4.5.1 Apixaban Dosing	Increase weight range table to include weight tiers of 3 to < 4 kg, 4 kg to < 5 kg, 5 kg to < 6 kg	Describe the additional weight tiers for apixaban dosing
Body; Section 4.5 Selection and Timing of Dose	Add mixing instructions for the use of the 0.1 mg apixaban capsule	Mixing instructions for apixaban formulation

Summary of key changes for Revised Protocol 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Body; Table 5.1.1 Flow Chart/Time and Events Schedule	Add 6 week visit for children < 3 months of age to get a weight and adjust dosing if needed	Adjust apixaban dosing
Body; Section 5.5 PK and PD; Table 5.5.1 for children 1 to < 18 years of age	Replace 1.0 ml blood collection tube with a 1.4 ml tube thereby increasing the total blood volume by 1.6 ml	Sourcing issues require replacing 1.0 ml tube with a 1.4 ml tube
Body; Section 5.5 PK and PD; Table 5.5.2 and 5.5.3	Add sampling schedule for children aged 3 months to < 1 year and ages 28 days to < 3 months	Provide clarity on the sampling schedule for all ages
Appendices; Appendix 1 Blood Sampling for Ages 3 months to < 18 years	Replace 1.0 ml blood collection tube with a 1.4 ml tube thereby increasing the total blood volume by 3.2 ml	Due to sourcing issues replaced 1.0 ml tube with a 1.4 ml tube
Appendices; Appendix 1 Blood Sampling; Table 2	Add sampling schedule for children ages 28 days to < 3 months	Provide clarity on the sampling schedule for all ages
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized

Overall Rationale for Revised Protocol 02, dated 07-Jun-2019:

The main reason for revising the protocol is to ensure that subjects are receiving the expected study treatment duration of 12 months. This resulted in the definition of a month being changed from 28 days to 30 days. The visit schedule was also revised to ensure 12 months of treatment. The sample size has been increased by 50 patients to 200 to account for those patients who completed the study with less than one year of treatment duration. Additionally, the statistical tables have been revised to account for the increased sample size. The exclusion criteria was revised for those patients with a known inherited or acquired thrombotic disorder. Additionally, minor administrative changes will be incorporated

The revised protocol applies to all future participants and to all participants currently enrolled.

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis 6th paragraph	Added following text at the end of the paragraph 'Drug diaries will be used to record administration of study medication'.	Reinforce collection of patient diaries
Synopsis Study Design; 2nd paragraph	Increased sample size from 150 to approximately 200 subjects and adjusted patient numbers in each treatment arm accordingly	To ensure that a 12 month treatment duration is achieved
Synopsis Study Design; 3rd paragraph	Defined a month as 30 days when calculating visit schedule	To ensure that a 12 month treatment duration is achieved
Synopsis Study Design; 4th paragraph	Defined the study visit schedule as starting from Day 1	To ensure that a 12 month treatment duration is achieved
Synopsis Study Population, 3rd paragraph	Described the timeline of opening enrollment to various ages	To provide the timeline of when specific age of children could be enrolled
Synopsis Key exclusion criteria, item #16	Added criteria 'Known inherited or acquired thrombotic disorders (eg, antiphospholipid syndrome [APS])'	To provide additional safety precautions to the study
[redacted]		
Synopsis Table 1.4-1 Apixaban Doses for Ages 3 Months to < 18 Years	Re-worked table to list weight ranges from lowest to highest	Make table easier to read
Synopsis Statistical Considerations, Sample Size, second paragraph	Increased sample size from 150 to approximately 200 subjects and adjusted patient numbers in each treatment arm accordingly	To ensure that a 12 month treatment duration is achieved
Synopsis	Deleted last sentence 'Safety analyses will	Statement already stated in

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Statistical Considerations, Analyses	be based on safety population. Efficacy analyses will be based on intention to treat (ITT) population'.	synopsis
Section 1.4 Product Development Background, Apixaban Dose Selection, Table 1.4-1	Re-worked table to list weight ranges from lowest to highest	Make table easier to read
Section 3.1 Study Design and Duration, first paragraph	Increased sample size from 150 to approximately 200 subjects and adjusted patient numbers in each treatment arm accordingly	To ensure that a 12 month treatment duration is achieved
Section 3.1 Study Design and Duration, second paragraph	Added following text at the end of the paragraph 'Drug diaries will be used to record administration of study medication'.	Reinforce collection of patient diaries
Section 3.1 Study Design and Duration, third paragraph	Defined a month as 30 days when calculating visit schedule	To ensure that a 12 month treatment duration is achieved
[redacted]		
Section 3.1 Study Design and Duration, Treatment Period; first paragraph	Defined the study visit schedule as starting from Day 1	To ensure that a 12 month treatment duration is achieved
Section 3.1 Study Design and Duration, Duration; second paragraph	Described the timeline of opening enrollment to various ages	To provide the timeline of when specific age of children could be enrolled
Section 3.3.2 Exclusion Criteria, Item 2 Medical History and Concurrent Diseases, Item 'g'	Added criteria 'Known inherited or acquired thrombotic disorders (eg. antiphospholipid syndrome [APS])'	To provide additional safety precautions to the study
Section 4.5 Selection and Timing of Dose for Each Subject, Eighth paragraph	Added following text at the end of the paragraph 'Drug diaries will be used to record administration of study medication'.	Reinforce collection of patient diaries
Section 4.5 Selection and Timing of Dose for Each Subject, Table 4.5-1	Re-worked table to list weight ranges from lowest to highest	Make table easier to read
Table 5.1-1, Study Drug Supplies	Add the dispensation of patient diaries at the randomization visit	Reinforce collection of patient diaries
Table 5.1-2, Study Drug Supplies	Relabeled columns of 'During Treatment and Follow Up	Provide more clarity around study visits
Table 5.1-2	Added collect Body weight at final visit	Need Body weight at final visit
Table 5.1-2, Study Drug	Added collection of patient diaries at all	Reinforce collection of patient

Summary of key changes for Revised Protocol 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	the office visits during the treatment period	diaries
Section 8.1 Sample Size Determination, second paragraph	Increased sample size from 150 to approximately 200 subjects and adjusted patient numbers in each treatment arm accordingly	To ensure that a 12 month treatment duration is achieved
Table 8.1-1, Table 8.1-2, Table 8.1-3, Table 8.1-4, and Table 8.1-5	Revised in the table the number of safety events, event rate, 95% confidence, and Power calculations interval due to the increase of sample size of 200 for each arm	Table adjustment due to increase in sample size
All	Minor formatting and typographical corrections	Minor, therefore have not been summarized