Official Title of Study:

A Randomized, Open-Label, Active Controlled, Safety and Descriptive Efficacy Study in Pediatric Subjects Requiring Anticoagulation for the Treatment of a Venous Thromboembolic Event

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A RANDOMIZED, OPEN-LABEL, ACTIVE CONTROLLED, SAFETY AND DESCRIPTIVE EFFICACY STUDY IN PEDIATRIC SUBJECTS REQUIRING ANTICOAGULATION FOR THE TREATMENT OF A VENOUS THROMBOEMBOLIC EVENT

Compound:	PF-04652577 (BMS-562247)
Compound Name:	Apixaban
USA IND Number:	IND 66,106
European Clinical Trial Database (EudraCT) Number:	2014-002606-20
Pfizer Protocol Number: **Bristol-Myers Squibb Protocol Number**	B0661037 CV185-325
Phase:	4 (Phase 2 or 3 if so designated by local regulation)

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 8	28 April 2022	1. Study Design section, Section 3 and Section 9.1 all updated for the neonate group sample size determination. Changed approximately to "up to". Section 3 added completion date of age group 3 and mentions the focus is now on enrolling the neonate cohort. 2. Section 4.1 Inclusion Criteria: removed the 5 day requirement for tolerating feeding, if subject is tolerating medications enterically. 3. Section 4.2 Exclusion Criteria: clarified that SOC is limited to heparins or DTIs for neonates. 4. Section 5, Table 3. Study Treatments: added text to footnote 'a' to clarify that neonate subjects (birth to ≤27 days) will be assigned and treated with apixaban only. 5. Section 5.1 Allocation to Treatment: updated for the neonate group sample size determination. 6. Section 5.2.2 Preparation and Dispensing: updated the mediums used for apixaban 0.1 mg sprinkle capsule. 7. Section 5.2.4 Compliance section updated. 8. Section 7.2.2 Blood Volume Collection: updated the blood volume collection for neonates including a new Table 5a for neonates. 9. Section 7.4.1 Sampling Timepoint updated indicating local hematocrit result needed for all DBS PK sampling. 10. Section 7.8.2 typo corrected. 11. Section 8 Assessment of Intensity for

		adverse events was added. 12. Section 8.5 typo corrected for medication error. 13. Section 9.2 Efficacy Analysis: updated age strata to age group. 14. Section 9.3 Safety Analysis: updated to clarify that a summary of the overall results as well as summaries for each age group will be included. 15. Section 9.4 Pharmacokinetic and Pharmacodynamic Analyses: updated to reference a separate analysis plan.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Abbreviations

This is a list of abbreviations that may or may not be used in the protocol.

Abbreviation	Term
ACCP	American College of Chest Physicians
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BMS	Bristol-Myers Squibb
BP	blood pressure
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
CT	computerized tomography
CTA	clinical trial application
CVAD	central venous access device
CVC	central venous catheter
DILI	drug induced liver injury
DMC	data monitoring committee
DTI	Direct thrombin inhibitor
DVT	deep vein thrombosis
EAC	Endpoint Adjudication Committee
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDMC	external data monitoring committee
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FFP	fresh frozen plasma
FSH	follicle-stimulating hormone
FXa	activated factor X

Abbreviation	Term
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HR	heart rate
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISTH	International Society on Thrombosis and Haemostasis
IUD	intrauterine device
L	liter
LFT	liver function test
LMWH	low molecular weight heparin
LP	lumbar puncture
LSLV	last subject last visit
MRI	magnetic resonance imaging
N/A	not applicable
NHBPEP	National High Blood Pressure Education Program Working Group
NONMEM	nonlinear mixed effects modeling
PCC	prothrombin complex concentrate
PD	pharmacodynamics
PE	pulmonary embolism
P-gp	P-glycoprotein
PK	pharmacokinetic
PPK	population pharmacokinetic
PT	prothrombin time
PTS	post thrombotic syndrome
SAE	serious adverse event
SC	subcutaneous
SGPT	serum glutamic-pyruvic transaminase
SOA	Schedule of Activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
UFH	unfractionated heparin
ULN	upper limit of normal
US	ultrasound
USA	United States of America
VKA	vitamin K antagonist
VTE	venous thromboembolism
WOCBP	women of childbearing potential

PROTOCOL SUMMARY

Background and Rationale:

The results of both the AMPLIFY and AMPLIFY-EXT trials show that apixaban is a safe and efficacious alternative to current standards of care without the need for parenteral administration or monitoring. Currently there are three main classes of anticoagulants used for the treatment of venous thromboembolism (VTE), which are well established and approved in adults, but are not approved for use in children: Vitamin K Antagonists (VKA) (eg, warfarin), unfractionated heparin (UFH), and low molecular weight heparin (LMWH), with the exception of one LMWH, FRAGMIN® (dalteparin sodium) injection.[31] Through extrapolation of the adult data, physicians are using these anticoagulants in children. The recommended therapeutic international normalized ratio (INR) ranges for VKA in children are directly extrapolated from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children. Thus, for most indications, the therapeutic target INR is 2.5 (range, 2.0-3.0). The unfractionated heparin (UFH) dose is selected based on activated partial thromboplastin time (aPTT) therapeutic ranges universally determined using plasma: aPTT by protamine titration of 0.2 to 0.4 units/mL or an anti-Factor Xa (FXa) level of 0.35 to 0.7 units/mL. Therapeutic ranges for low molecular weight heparin (LMWH) are extrapolated from adults and based on anti-factor Xa (anti-FXa) levels. The guideline for therapeutic LMWHs being given subcutaneously twice daily is an anti-FXa level of 0.50 to 1.0 units/mL in a sample taken 4 to 6 hours following a subcutaneous injection. Using the same concept of extrapolation, this study will extrapolate efficacy based on achievement of exposure in children ≥28 days of age similar to that with the AMPLIFY regimen of 10 mg twice daily for the first 7 days and then 5 mg twice daily thereafter in adults. For the study's pharmacokinetic (PK) neonate cohort, subjects ≤27 days of age, who will have been treated with standard of care therapies for 5 to 14 days prior to randomization, the dose will be targeted to achieve an exposure similar to 5 mg twice daily in adults. For the study's post-PK neonate cohort (ie, those neonates recruited after the PK sub-analysis is completed), which may be treated with standard of care therapies for up to 14 days prior to randomization, the dose will be targeted to achieve an exposure similar to 10 mg twice daily in adults for the first week, and 5 mg twice daily thereafter.

Study Objectives:

- Primary: To assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE;
- Secondary: To evaluate apixaban pharmacokinetic (PK) and anti-FXa activity in pediatric subjects requiring anticoagulation for the treatment of a VTE.

Study Endpoints:

- Primary Safety: The composite of major and clinically relevant non-major bleeding;

- Primary Efficacy: A composite of: (i) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism and (ii) VTE-related mortality.

Study Design:

Treatment assignment will not be blinded. Up to 250 subjects will be randomized into the trial using a ratio of 2 to 1 to apixaban or standard of care (SOC), respectively. A goal of 30 or more subjects will be randomized into each of the following 3 age groups to be used for analysis: (1) 12 to <18 years; (2) 2 to <12 years; (3) 28 days to <2 years; For age group 4, neonates (birth to ≤27 days), the sample size may be adjusted based on a PK sub-analysis that will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. The number of neonates on apixaban will not exceed 20 subjects.

Subjects 28 days of age or older may receive up to 14 days of standard anticoagulant treatment prior to randomization. Subjects will be monitored for laboratory safety parameters. Pre- and post-dose blood samples for peak and trough apixaban concentrations (PK) and anti-FXa activity levels (Pharmacodynamic, PD) will be obtained.

Radiologic imaging will be performed, and adjudicated, to confirm the index event (ie, primary diagnosis of thromboembolic event which will be treated with apixaban or SOC in this study). For subjects 2 years of age or older, in addition to the radiologic images obtained to confirm the index event, new radiologic images of the clot will be obtained at approximately the mid-point and end of treatment (EOT) visits. For subjects 28 days to <2 years of age and neonates (birth to ≤27 days of age) imaging should be performed at the EOT. All of the aforementioned images will be adjudicated. Additional imaging assessments can be performed at any time during the study, at the discretion of the investigator. In addition, when medically appropriate, new radiologic images will be obtained if recurrent VTE is suspected.

The palatability of the apixaban 0.5 mg tablet and 0.1 mg sprinkle capsule will also be assessed.

Study Treatment:

Subjects 2 years of age or older, randomized to the apixaban arm will receive open-label apixaban for 12 weeks. Subjects less than 2 years of age may receive open-label apixaban for 6 to 12 weeks as the Investigator deems is appropriate. For this population the duration of treatment is consistent with the recommendation of 2012 American College of Chest Physicians (ACCP) pediatric guidelines, 2018 American Society of Hematology (ASH) pediatric guidelines, and clinical experience and recommendation.[22,23] Enrollment will start with the oldest age group, and as pharmacokinetic (PK) data are obtained for the younger age groups in the single dose CV185118 PK study, the PK modeling and simulation results will be updated and used to support dosing recommendations for the younger age groups. An

approved amended protocol will be implemented prior to enrollment of each subsequent age group and the dose rationale will be described in an appendix.

The modeling and simulation results, described in Appendix 3 and Appendix 4, support the current dosing recommendation of fixed-dose body weight-tiered regimen for pediatric subjects aged 28 days to <18 years (Age Groups 1, 2, 3 in Table 1). As of May 2019, enrollment to Age Groups 1 and 2 was completed, and as of December 2020 enrollment to age group 3 was completed. This protocol amendment continues enrollment to the youngest age group, Group 4 (neonates, birth to ≤27 days). The age groups used for analysis will remain as Age Group 1: 12 to <18 years; Age Group 2: 2 to <12 years; Age Group 3: 28 days to <2 years; Age Group 4: neonates (birth to ≤27 days). Appendix 4 describes additional analyses performed to select doses in subjects 28 day to 3 months and complements Appendix 3. Appendix 3 supersedes Appendix 2 and Appendix 1. The fixed-dose, body weight-tiered regimen for all age groups is outlined in Table 1. Appendix 5 describes additional analyses performed to select an initial dose for neonates (birth to ≤27 days). Appendix 5 complements Appendix 3 and Appendix 4.

The enrollment of neonates and the dosing of neonates, will proceed as follows:

After being treated with standard of care therapies for from 5 to 14 days, all neonates in the PK cohort randomized to apixaban in Group 4 will receive apixaban 0.1 mg twice daily, prior to the completion of a PK sub-analysis described below. For these neonates, a series of blood samples will be collected after the first 0.1 mg dose of apixaban to predict each subject's daily apixaban exposure (AUCs) at steady-state. If the subject's predicted AUCss is outside the interval of 1293 to 4807 ng*hr/mL (90% prediction interval from adults with 5 mg twice daily), apixaban dose will be adjusted to remain within this interval. Further details are included in Appendix 5.

A PK sub-analysis will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. Neonates who continue to be recruited, while this PK sub-analysis is ongoing, will still require PK measurements and potential dose adjustments, until the results of the sub-analysis and final dose determination have been completed.

If the PK sub-analysis confirms that the 0.1 mg twice a day (BID) apixaban dose regimen is suitable for the post-PK neonates the ongoing recruitment of neonates will continue, with a dose of 0.2 mg BID apixaban for Days 1 to 7, followed by 0.1 mg BID, thereafter. Should the PK sub-analysis determine that a different dosing paradigm is appropriate, a subsequent protocol amendment will be required.

Table 1. Apixaban Doses for Age Groups 1, 2, 3, and 4†[a]

Age Group	Age	Body Weight	Days 1-7	Day 8 and Thereafter
1-3	28 days to <18 years[b]	≥35 kg	10 mg twice daily	5 mg twice daily
		<35 to 25 kg	8 mg twice daily	4 mg twice daily
		<25 to 18 kg	6 mg twice daily	3 mg twice daily
		<18 to 12 kg	4 mg twice daily	2 mg twice daily
		<12 to 9 kg	3 mg twice daily	1.5 mg twice daily
		<9 to 6 kg	2 mg twice daily	1 mg twice daily
		<6 to 5 kg	1 mg twice daily	0.5 mg twice daily
		<5 to 4 kg	0.6 mg twice daily	0.3 mg twice daily
4 – PK cohort	Neonates[c]	≥2.6 kg	0.1 mg twice daily or as determined by PK measurements[d]	0.1 mg twice daily or as determined by PK measurements[d]
4 – post-PK cohort[e]	Neonates[c]	<4 to 2.6 kg	0.2 mg twice daily	0.1 mg twice daily

a. Investigational product will be administered in accordance with the instructions provided.

b. Subjects enrolled in Age Group 3, 28 days to <2 years (a minimum of 4 kg) and <35 kg may be administered 0.5 mg tablets or 0.1 mg sprinkle capsules based on the assigned apixaban dose.

c. Neonates are defined as infants from birth up to ≤27 days of life. For pre-term infants born between 34 and <37 weeks gestation, investigators have the option to define the 27 day neonatal period starting from the actual date of birth (post-natal age) or may choose to define the 27 day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reaches 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4.

d. Neonate dose may be modified during PK-sub-analysis period until a fixed dose is determined. If a subject is randomized as part of the neonate cohort and subsequently reaches an age of 28 days or older and a weight of greater than or equal to 4 kg, the subject's dose beyond Day 8 will be adjusted, to align with the <5 to 4 kg body weight group, as defined above, at a dose of 0.3 mg twice daily, unless the subject in the PK cohort had a dose decrease on the basis of Day 1 PK measurements. Subjects who reach an age of 28 days or older and who have a weight less than 4 kg, should remain on their initial neonate dose, or on the dose determined by the day 1 PK measurement, when that information becomes available.

e. Should the PK sub-analysis reveal dosing different from 0.1 mg BID, a subsequent protocol amendment will be required.

† An amended protocol will be implemented prior to enrollment of each subsequent age group and the dose rationale will be described in an appendix.

Age Group to be used for analyses: Age Group 1:12 to <18 years; Age Group 2: 2 to <12 years; Age Group 3: 28 days to <2 years; Age Group 4 = Neonates (birth to ≤27 days).

Subjects randomized to the SOC arm will receive a dose and dosing regimen of anticoagulation treatment based on usual and customary care per local practices and that will be aligned with the current, internationally recognized ACCP and ASH guidelines, or equivalent, for at least 12 weeks.[22,23] Subjects less than 2 years of age may receive SOC for 6 to 12 weeks, consistent with the ACCP and ASH guidelines.[22,23] Monitoring of SOC will

be based on usual and customary care per local practices and should be aligned with the current guidelines.

Statistical Method:

Efficacy and safety outcomes will be presented using descriptive statistics including but not limited to means and standard deviations for continuous variables along with counts and frequencies for discrete variables.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activity	**Screening[c]**	**Day 1[c]**	**Day 14**	**Day 28[d]**	**Day 42[j]**	**Day 63[d]**	**Day 84 End of Treatment (EOT)[j]**	**Follow- Up 35 Days post EOT[d]**
Visit Window (Days) (Study Days)	Day -7 up to and including Day 1	0	-7 (7 to 14)	±7 (21 to 35)	±7 (35 to 49)	±7 (56 to 70)	±7 (77 to 91)	±5 (EOT + 30 to 40)
Informed consent/assent	X							
Confirm inclusion/exclusion criteria	X[i]	X[i]						
Medical history	X							
Physical examination[a]	X		X[m]		X[m]		X[m]	
Laboratory								
Central/Local Laboratory Hematology[i]		X			X			
Central/Local Laboratory Blood Chemistry[i]		X			X			
Pregnancy test	X	X	X		X		X	
Prior or concomitant medication	X[e]	X[e]	X		X		X	
Randomization		X						
Study treatment								
Dispense and confirm subject/caregiver understanding of dosing instructions[r]		X	X		X			
Administer first dose of investigational product[o,p]		X						
Collect apixaban containers			X		X		X	
Assess compliance			X		X		X	
Assessments								
Confirm and document contraception use[k]	X	X	X	X	X	X	X	X
Submit radiologic images of the index event		X----------X						
Radiologic reassessment of index event (Allowed visit window)					X[h,j,l] (28 to 56)		X[l]	
Assess palatability of apixaban			X					
Adverse events[n]	Serious AEs only	X	X	X	X	X	X	X
Pharmacokinetic/Pharmacodynamic			X[f]		(X)[g]			
Pharmacokinetic sampling for Neonate PK Cohort		X[f]						

Extension Phase: Protocol Activity	Day 105[d]	Day 126 (EOT 6-week)[q]	Day 147[d]	Day 168 (EOT 12-week[q]	Follow- Up 35 Days post EOT[d]
Visit Window (Days) (Study Days continued from SOA)	±7 (98 to 112)	±7 (119 to 133)	±7 140 to 154)	±7	±5 (EOT + 30 to 40)
Physical examination		X[m]		X[m]	
Laboratory					
Central/Local Laboratory Hematology		X		X	
Central/Local Laboratory Blood Chemistry		X		X	
Pregnancy test[b]		X		X	
Prior or concomitant medication		X		X	
Study treatment					
Dispense and confirm dosing instructions[r]		X			
First dose of investigational product					
Collect apixaban containers		X		X	
Assess compliance		X		X	
Assessments					
Confirm and document contraception use[k]	X	X	X	X	X
Radiologic reassessment of index event[s] (Allowed visit window)		X[l]		X[l]	
Adverse events[n]	X	X	X	X	X

a. Perform physical examination including height/body length, weight, vital signs. Weight should be rechecked at an unplanned visit when the subject reaches 28 days of age, for the purposes of determining whether the subject's dose should be modified. If there is a 20% change in weight for subjects less than 2 years old, the investigator may contact the study Sponsor to discuss a possible change in dosing regimen.

b. For females of childbearing potential. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

c. Screening activities may be combined with Day 1 activities.

d. Visit can be conducted by telephone or on site.

e. Includes medication administered up to 30 days prior to randomization. Standard of care to treat the index event may be given up to 14 days prior to randomization into this study.

f. Refer to Section 7.4.1 Sampling Time Points for detailed instructions and Section 7.2.2 for special requirements when a dried blood spot blood collection method is used.

g. If one or both samples were not drawn during the Day 14 visit, then the Day 14 visit procedure should be repeated at the Day 42 visit to obtain the missing sample(s). Otherwise, samples are not required at the Day 42 visit.

h. Radiologic reassessment of the index event may occur anytime between Days 28 and 56.

i. The following laboratory tests are required to satisfy the exclusion criteria for this study and should be analyzed by the local laboratory and reviewed prior to randomization: platelets, serum creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), conjugated bilirubin, and pregnancy test when applicable. Only the most recent laboratory results, obtained within 7 days prior to randomization, may be used to satisfy this requirement. For subjects <2 years of age, labs may be evaluated using a local laboratory test and documented on the Local Lab CRF, in place of central laboratory tests for subsequent visits if all specified measures have been collected and reported.

j. For neonates and subjects <2 years of age receiving 6 weeks of study treatment, Day 42 and Day 84 (EOT) visits will be combined.

k. If contraception use is required according to Section 4.3 Life Style Guidelines.

l. Radiologic images that require sedation and/or radiation at the Day 42 or Day 84 (EOT) visits (if applicable, also applied to images obtained at Day 126 or Day 168 EOT visit) are not required and may be omitted, if not medically necessary.

m. Perform targeted physical exam as described in Section 7.1 Physical Examination.

n. During the screening period, assess only serious adverse events that occur after obtaining written informed consent and before the first dose of investigational product. Assess all adverse events and serious adverse events that occur after the administration of the first dose of investigational product.

o. For subjects already on anticoagulation treatment at study start and randomized to apixaban, the first dose of apixaban may be administered at home to comply with other protocol and safety procedures.

p. Investigational product will be administered in accordance with the instructions provided.

q. Subjects randomized to apixaban may continue to receive apixaban treatment for 6 or 12 weeks in the Extension Phase. End of Treatment activities should be completed at Day 126 or Day 168.

r. A qualified site staff member shall review the dosing instructions with the subject/caregiver and understanding of these instructions. Subjects/caregivers shall be educated on changes in dosing for Day 8 and beyond. On Day 7 subjects/caregivers shall be contacted to remind them of the dosing change if possible. This interaction shall be noted in the source document.

s. Additional imaging assessments can be performed at the discretion of the Investigator, at any time during the study.

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APPENDICES

1. INTRODUCTION

Venous Thromboembolism (VTE) is rare in the pediatric population in comparison to the adult population. In 1994, the Canadian Registry of VTE in children older than 1 month reported a VTE incidence of 0.07 per 10,000 children per year and 5.3 per 10,000 hospitalizations per year, as compared with a range of 2.5 to 5 cases per 100 adults. However, in the past decade, increased survival of children with serious illnesses and improved diagnostic techniques have led to an increasing awareness of the occurrence and sequelae of VTE in the pediatric population. A recent multicenter study demonstrated a dramatic increase in the diagnosis of VTE at children's hospitals from 2001 to 2007. During that 7-year period, 11,337 hospitalized patients were diagnosed with VTE where the annual rate of VTE increased by 70% from 34 to 58 cases per 10,000 hospital admissions [Raffini et al, 2009].[25]

Children and adults are thought to share a common basic pathophysiology of venous thrombosis based on Virchow's triad. Venous stasis, vascular injury, and hypercoagulability all predispose to thrombosis. In adults, several risk factors are known to invoke one or more of the Virchow conditions. These include prolonged immobilization, the presence of a central venous line, surgery, trauma, malignancy, pregnancy and puerperium, treatment with oral contraceptives, hormone replacement therapy, presence of antiphospholipid antibodies, and inherited disorders of coagulation. The pathophysiology of VTE in children is similar, but the contribution of each factor differs among age groups [Albisetti et al, 2012].[3]

Differences between adult and pediatric coagulation factor values are variable: some factors are present at adult levels or higher from birth, while others are extremely low, rising to adult values only in adolescence. The mean values for fibrinogen, factor (F) V, FVIII, von Willebrand factor, and FXIII are >70% of adult values at birth. However, for both premature and healthy full-term infants, the mean values for the contact factors and vitamin K-dependent factors are <70% of adult values; and while increasing throughout childhood, they remain low, compared to adult levels, even into adolescence. The coagulation inhibitors, antithrombin (AT), heparin cofactor II (HCII), protein C, and protein S, are also decreased at birth. AT and HCII reach adult levels around 6 months of age, whereas protein C and protein S plasma levels reach adult levels only in adolescence. Two other coagulation inhibitors, α2-macroglobulin and protein C1 inhibitor are increased at the time of birth, compared to adult levels, and remain elevated until adulthood.

Several factors likely contribute to the lower incidence of VTE in children compared with that in adults. Certainly, the unique hemostatic physiology of infancy and childhood has an impact. Also important is the integrity of the vessel wall and its influence on thrombosis. The vascular endothelium of children has not accumulated damage from hypertension, diabetes, or hypercholesterolemia, and so maintains anticoagulant properties. Similarly, most children have not been exposed to acquired thrombotic risk factors such as oral contraceptives or smoking, and they are much less frequently exposed to antiphospholipid antibodies or malignancies. Nonetheless, thromboembolisms do occur in children. It must be understood that there are differences in the causes of VTE, when comparing older children to younger children and neonates. As described in the 2018 American Society of Hematology 2018 Guidelines for management of VTE:[23] treatment of pediatric VTE: "The

commonest age groups for VTE are neonates and teenagers, and this reflects the pattern of associated underlying diseases and interventions. The most common precipitating factor is the presence of a central venous access device (CVAD), which is related to almost 90% of VTE in neonates and 60% in older children".[4]

Thromboembolism is a well-recognized complication of cancer in children. There are several factors which contribute, including the presence of a central venous catheter (CVC), the underlying malignancy, dehydration, and infection [Macartney et al, 2011].[18]

Primary and secondary antiphospholipid syndrome results in an increased risk of deep vein thrombosis (DVT), acute coronary syndrome, and transient ischemic attack. In children, there is a long-term risk of recurrence following thrombosis, without long-term anticoagulation [Macartney et al, 2011].[18]

Though inherited thrombophilia can play a role in VTE events in children, it is not as well understood as in the adult population, partly due to lack of studies; therefore, the significance is not clear [Macartney et al, 2011].[18]

Once a VTE occurs, the progression of the disease and the aim of antithrombotic therapy are the same for both adults and children. They are to: 1) reduce the risk of death due to thrombus extension or embolization; 2) reduce the incidence of recurrent thrombosis; 3) reduce the incidence of post thrombotic syndrome by limiting vascular damage; and 4) maintain vessel patency and vascular access [Chalmers et al, 2011].[7]

Although much is known about the factors underlying the risk for recurrence of VTE in adults, little is known about these risks in children. In children that have an underlying acquired risk factor for VTE (a CVC or underlying medical condition), recurrence is uncommon if the underlying cause is removed. In a study involving 153 consecutive neonates and children with VTE, 91 percent had an underlying medical condition and 77 percent had a CVC [Revel-Vilk et al, 2003].[26] The risk of VTE recurrence in this study was 10.5 percent; in all children, the same acquired risk factor was present in the first and the recurrent episode of VTE. In this population, the presence of a prothrombotic state or an elevated level of factor VIII was not associated with recurrence [Albisetti et al, 2012].[3]

In children, particularly neonates, approximately two-thirds of VTEs are associated with the use of CVCs or access devices, which can impair vascular access and require intervention or lead to embolization [Andrew et al, 1994; van Ommen et al, 2001; Kuhle et al, 2004].[4,29,14] CVCs are extremely important for the long- and short-term management of pediatric patients with a variety of severe diseases (eg, total parenteral nutrition; intensive fluid management; administration of blood products, antibiotics, and chemotherapy). Most CVC-associated VTEs occur in the upper venous system, in association with CVCs inserted percutaneously through a jugular or subclavian vein [Massicotte et al, 1998].[19] Femoral venous catheters are used less commonly but also can be associated with VTE [Worly et al, 2004].[30]

Treatment of VTE

Anticoagulation in children may be administered prophylactically to prevent thrombosis in high-risk individuals or in therapeutic doses in those with confirmed thrombosis. The most comprehensive guidelines for the treatment of pediatric VTE published are those of the internationally recognized American College of Chest Physicians (ACCP) and American Society of Hematology(ASH).[22,23] The decision to anticoagulate will depend on each individual situation, weighing the benefits against the risk of bleeding. As in adults, anticoagulation therapy is administered to prevent clot extension or embolization, to reduce the risk of recurrence, to prevent long-term complications of vascular compromise such as post thrombotic syndrome (PTS), and to maintain blood vessel patency for long-term venous access [Macartney et al, 2011].[18]

Since there is no one standard of care (SOC) for all children for the treatment of VTE, the recommendation in the current ASH guidelines and ACCP guidelines (2012) includes use of unfractionated heparin (UFH), low molecular weight heparin (LMWH), and/or a vitamin K antagonist (VKA). For subjects 28 days to <2 years of age, this study will limit SOC to heparin only (ie, UFH or LMWH). For neonates (birth to 27 days), they will be assigned and treated with apixaban only.

1.1. Indication

Apixaban (PF-04652577, BMS-562247-01, Eliquis) is an orally active factor Xa (FXa) inhibitor that is being developed by Pfizer and Bristol Myers Squibb (BMS) for the treatment of venous thromboembolism in children.

1.2. Background and Rationale

Apixaban (BMS-562247) is an orally active, direct inhibitor of FXa that binds to the active site of FXa and inhibits its activity without requiring antithrombin. A comprehensive summary of the pharmacology, absorption, distribution, metabolism, and excretion (ADME), toxicology and clinical experience with apixaban are provided in the Investigator Brochure (IB).

Marketing authorization for apixaban has been granted for the prevention of venous thromboembolism (VTE) in adults who have undergone elective hip or knee replacement surgery and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults in the United States of America (USA), the European Union (EU), Canada, and other countries, and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in the USA, EU, Canada, Japan, and other countries worldwide.

Efficacy and safety for the treatment of VTE have been demonstrated in 2 completed pivotal Phase 3 studies (CV185056, AMPLIFY and CV185057, AMPLIFY-EXT). Apixaban was studied in a randomized, double-blind, triple dummy trial (AMPLIFY) that compared apixaban (10 mg twice daily for seven days followed by 5 mg twice daily) with conventional anticoagulation (warfarin for six months co-administered with subcutaneous (SC) enoxaparin for at least the first five days and until an INR of 2 was achieved) in 5395 adult subjects for

the treatment of acute symptomatic proximal DVT only or pulmonary embolism (PE) with or without a DVT. The published results [Agnelli, G et al, 2013][2] are as follows:

- The primary efficacy outcome occurred in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18; difference in risk [apixaban minus conventional therapy], −0.4 percentage points; 95% CI, −1.3 to 0.4). Apixaban was noninferior to conventional therapy (P<0.001) for predefined upper limits of the 95% confidence intervals for both relative risk (<1.80) and difference in risk (<3.5 percentage points). Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received conventional therapy (relative risk, 0.31; 95% CI, 0.17 to 0.55; P<0.001 for superiority). The composite outcome of major bleeding and clinically relevant nonmajor bleeding occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; P<0.001). Rates of other adverse events (AE)s were similar in the two groups.

In support of these results, apixaban was also studied in a randomized, double-blind trial (AMPLIFY-EXT) that compared the efficacy and safety of two doses of apixaban (2.5 mg or 5 mg twice daily for 12 months) to placebo in 2482 subjects with a VTE who reached clinical equipoise after completing 6 to 12 months of anticoagulation for their index event. The published results [Agnelli, G et al, 2013][1] are as follows:

- A total of 2486 patients underwent randomization, of whom 2482 were included in the intention-to-treat analyses. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 73 of the 829 patients (8.8%) who were receiving placebo, as compared with 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% confidence interval [CI], 5.0 to 9.3) and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1) (P<0.001 for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.

The results of both the AMPLIFY and AMPLIFY-EXT trials show that apixaban is a safe and efficacious alternative to current standards of care without the need for parenteral administration or monitoring.

Currently there are three main classes of anticoagulants used for the treatment of VTE, which are well established and approved in adults, but are adapted yet not approved for use in children: VKA (eg, warfarin), UFH, and LMWH, with the exception of one LMWH, FRAGMIN® (dalteparin sodium) injection.[31] Through extrapolation of the adult data, physicians are using these anticoagulants in children. The recommended therapeutic INR

ranges for VKA in children are directly extrapolated from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children. Thus, for most indications, the therapeutic target INR is 2.5 (range, 2.0-3.0) [Monagle et al, 2012].[22] The UFH dose is selected based on activated partial thromboplastin time (aPTT) therapeutic ranges universally determined using plasma: aPTT by protamine titration of 0.2 to 0.4 units/mL or an anti-FXa level of 0.35 to 0.7 units/mL [Monagle et al, 2012].[22] Therapeutic ranges for LMWH are extrapolated from adults and based on anti-FXa levels. The guideline for therapeutic LMWHs being given subcutaneously twice daily (BID) is an anti-FXa level of 0.50 to 1.0 units/mL in a sample taken 4 to 6 hours following a subcutaneous injection [Monagle et al, 2012].[22] Using the same concept of extrapolation, this study will extrapolate efficacy based on achievement of exposure in children similar to that with the AMPLIFY regimen of 10 mg twice daily for the first 7 days and then 5 mg twice daily thereafter in adults.

The safety and efficacy profile of apixaban (AMPLIFY and AMPLIFY-EXT trials) suggests a possible benefit of oral apixaban in children over standard of care for the treatment of VTE. This current pediatric VTE trial will enroll subjects who require anticoagulation for a newly diagnosed VTE. Subjects will be randomized to receive either apixaban or SOC. The primary objective of this study is to assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE with 12 weeks of therapy in subjects ≥ 2 years of age or 6 to 12 weeks of therapy in subjects <2 years of age.

1.2.1. Pharmacokinetics of Apixaban in Pediatric Subjects

Study CV185079 evaluated the multiple-dose pharmacokinetic (PK) and pharmacodynamic (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. Six subjects ranging from between the ages of 13 to 17 years of age were administered 0.66 mg/m^2 apixaban BID x 10 days and two subjects, ages [redacted] years of age were administered 0.60 mg/m^2 apixaban BID x 10 days.

Model-estimated steady state area under the curve over the dosing interval [$AUC_{(TAU)}$] measured 234.6 ng/mL in the six pediatric subjects from the ages of 13 years to17 years and 223.5 ng/mL for the two subjects of ages [redacted]. Apixaban was generally safe and well-tolerated by the 8 subjects in this study. There were no deaths, treatment-related Serious Adverse Events (SAE)s, or bleeding-related AEs reported.

The most frequently occurring AE and laboratory marked abnormality was prolonged aPTT. Prolongation of aPTT is a known pharmacological effect of direct acting FXa inhibitors and as noted above, aPTT prolongation was not associated with any bleeding events. Apixaban administration had no apparent impact on vital signs or physical examination findings.

Study CV185118 is a single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As data were obtained from the CV185118 study, the modeling and simulation results were updated and used to support dosing recommendations for each of the four pre-specified age groups of B0661037, in a

sequential fashion. Approved amended protocols were implemented prior to enrollment of each subsequent age group and the dose selection rationales were described in appendices.

To date, apixaban has been well tolerated, and there have been no significant apixaban-related safety findings in CV185118. Four interim analyses of PK data have been completed for Study CV185118.

- Interim analysis 1 used PK data from 16 subjects (5, 7, and 4 subjects within the 12 to <18, 6 to <12, and 2 to <6 years of age groups, respectively). The results showed that mean single-dose $AUC_{(INF)}$ in children across all age groups was generally similar to the median steady-state $AUC_{(TAU)}$ in adult patients treated with apixaban 2.5 mg BID for the prevention of venous thromboembolism. A linear relationship between apixaban concentration and anti-FXa activity was observed, which is consistent with that observed in adult subjects. The results of this analysis were used to support the dose selection rationale for Age Group 1, as described in Appendix 1, which is superseded by Appendix 3.

- Interim Analysis 2 used PK data from 28 subjects (8, 8, 8, and 4 subjects within the 12 to <18 years, 6 to <12 years, 2 to <6 years, and 9 months to <2 years of age groups, respectively). The results showed that the oral clearance increased with increasing age and reached values similar to those of adults in pediatric subjects older than 12 years. A linear relationship between apixaban concentration and anti-FXa activity was observed, which is consistent with that observed in adult subjects. The results of this analysis were used to support the updated dose selection rationale for Age Group 1 and the new dose selection rationale for Age Group 2, as described in Appendix 2, which is superseded by Appendix 3.

- Interim Analysis 3 used PK data from 34 subjects (8, 8, 8, 6 and 4 subjects within the 12 to <18 years, 6 to <12 years, 2 to <6 years, 9 months to <2 years and 28 days to <9 months of age groups, respectively). The results showed that the oral clearance increased with increasing age and reached values similar to those of adults in pediatric subjects older than 12 years. In addition, that oral clearance, when normalized to body weight, was constant across the pediatric age range of 3 months to 18 years. The results of this analysis were used to support the dose selection rationale for pediatric subjects with aged 3 months to <18 years, as described in Appendix 3.

- Interim Analysis 3C used PK data from 54 subjects (16, 11, 8, 9, and 1 subject within the 12 to <18 years, 6 to <12 years, 2 to <6 years, 9 months to <2 years, 28 days to <9 months, and <28 days of age groups, respectively) in CV185079 and CV185118. The results showed that the oral clearance increased with increasing age and reached values similar to those of adults in pediatric subjects older than 12 years. In addition, that oral clearance, when normalized to body weight, was constant across the pediatric age range of 28 days to 18 years. The results of this analysis were used to support the dose selection rationale for pediatric subjects ages 28 days to <3 months

of age, as described in Appendix 4, which is the most current and complements Appendix 3 since doses in subjects ≥3 months of age remain the same.

1.2.2. Pediatric Formulation Development

In April 2017, the Sponsor suspended use of the apixaban oral solution in children <5 years of age in pediatric studies, including B0661037, because the daily intake of [redacted] one of the key solubilizing agents in the apixaban oral solution formulation, would exceed the threshold specified in a 2014 draft European Medicines Agency (EMA) guideline for children <5 years of age.[10] The official EMA guidance was published in October 2017.[11]

In order to resume enrollment of pediatric subjects <5 years of age in ongoing studies, the Sponsor developed a 0.5 mg strength tablet of the currently approved adult formulation for use in subjects ≥3 months of age (and a minimum of 6 kg weight). The tablet is relatively [redacted] with approximately [redacted] weight. The composition (drug excipient ratios) and manufacturing process (up to compression) for the 0.5-mg tablet is [redacted] These 0.5-mg tablets also use the [redacted] and final blend as the [redacted]. Therefore, the 0.5-mg tablets have the same pharmaceutical characteristics as the apixaban [redacted] while being proportionally scaled to a lower strength for the pediatric use.

In addition to 0.5 mg strength tablets, the 0.1 mg sprinkle capsules will be available for use in pediatric subjects.

1.2.3. Dose Selection Age Groups 1, 2, and 3

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 2 and supported by Appendix 3 and Appendix 4.

The modeling and simulation results, described in Appendix 3 and Appendix 4, support the current dosing recommendation of fixed-dose body weight-tiered regimen for pediatric subjects aged 28 days to <18 years (Age Groups 1, 2,3 in Table 2). The age groups used for analysis will remain as Age Group 1: 12 to <18 years; Age Group 2: 2 to <12 years; Age Group 3: 28 days to <2 years; Age Group 4: neonates (birth to ≤27 days). Appendix 4 describes additional analyses performed to select doses in subjects 28 days to 3 months and complements Appendix 3. Appendix 3 superseded Appendix 2 and Appendix 1. The fixed-dose, body weight-tiered regimen for all age groups is outlined in Table 2.

1.2.4. Dose Selection for Age Group 4

After being treated with standard of care therapies for 5 to 14 days, all neonate subjects randomized to apixaban in the PK cohort of Group 4, will receive apixaban 0.1 mg twice daily, prior to the completion of a PK sub-analysis described below. For these neonates, a series of blood samples will be collected after the first 0.1 mg dose of apixaban to predict each subject's daily apixaban exposure (AUCss) at steady-state with 0.1 mg twice daily. If the subject's predicted AUCss is outside the interval of 1293 to 4807 ng*hr/mL

(90% prediction interval from adults with 5 mg twice daily), apixaban dose will be adjusted to remain within this interval. If the predicted exposure of neonate subjects randomized to apixaban in the PK cohort is above the 95th percentile, apixaban dose will be reduced to 0.1 mg daily. If the predicted exposure is below the 5th percentile, apixaban dose will be increased to 0.2 mg twice daily. If the 90% prediction interval cannot be achieved with either 0.1 mg daily or 0.2 mg twice daily, the subject will be discontinued from apixaban. Further details on dose selection rationale for initial 0.1 mg BID are included in Appendix 5.

A PK sub-analysis will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. Neonates who continue to be recruited, while this PK sub-analysis is ongoing, will still require PK measurements and potential dose adjustments, until the results of the sub-analysis and final dose determination have been completed.

If the PK sub-analysis confirms that the 0.1 mg BID apixaban dose regimen is suitable for the post-PK neonates the ongoing recruitment of neonates will continue, with a dose of 0.2 mg BID apixaban for Days 1 to 7, followed by 0.1 mg BID, thereafter. Should the PK sub-analysis determine that a different dosing paradigm is appropriate, a subsequent protocol amendment will be required.

If after the first week of treatment a subject that is randomized as a neonate subsequently reaches an age of 28 days or older and a weight of greater than or equal to 4 kg, the subject's dose will be adjusted one time, as clinically appropriate, to align with the <5 to 4 kg body weight group's Day 8 or thereafter dose, as defined in Table 2, unless the subject had a prior dose decrease, based on Day 1 PK measurements. Subjects who reach an age of 28 days or older and who have a weight less than 4 kg, should remain on their initial neonate dose, or on the dose determined by the Day 1 PK measurement, when that information becomes available.

Table 2. Apixaban Doses for Age Groups 1, 2, 3, and 4†[a]

Age Group	Age	Body Weight	Days 1-7	Day 8 and Thereafter
1-3	28 days to <18 years[b]	≥35 kg	10 mg twice daily	5 mg twice daily
		<35 to 25 kg	8 mg twice daily	4 mg twice daily
		<25 to 18 kg	6 mg twice daily	3 mg twice daily
		<18 to 12 kg	4 mg twice daily	2 mg twice daily
		<12 to 9 kg	3 mg twice daily	1.5 mg twice daily
		<9 to 6 kg	2 mg twice daily	1 mg twice daily
		<6 to 5 kg	1 mg twice daily	0.5 mg twice daily
		<5 to 4 kg	0.6 mg twice daily	0.3 mg twice daily
4 PK Cohort subjects	Neonates[c]	≥2.6 kg	0.1 mg twice daily or as determined by PK measurements[d]	0.1 mg twice daily[d]
4 Post-PK Cohort subjects[e]	Neonates[c]	<4 to 2.6 kg	0.2 mg twice daily	0.1 mg twice daily

a. Investigational product will be administered in accordance with the instructions provided.

b. Subjects enrolled in Age Group 3, 28 days to <2 years (a minimum of 4 kg) and <35 kg may be administered 0.5 mg tablets or 0.1 mg sprinkle capsules based on the assigned apixaban dose.

c. Neonates are defined as infants from birth up to ≤27 days of life. For pre-term infants born between 34 and <37 weeks gestation, investigators have the option to define the 27 day neonatal period starting from the actual date of birth (post-natal age) or may choose to define the 27 day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reaches 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4.

d. Neonate dose may be modified during PK-sub-analysis period until a fixed dose is determined. If a subject is randomized as part of the neonate cohort and subsequently reaches an age of 28 days or older and a weight of greater than or equal to 4 kg, the subject's dose beyond Day 8 will be adjusted to align with the <5 to 4 kg body weight group, as defined above, at a dose of 0.3 mg twice daily, unless the subject(s) in the PK cohort had a dose decrease on the basis of Day 1 PK measurements. Subjects who reach an age of 28 days or older and who have a weight less than 4 kg, should remain on their initial neonate dose, or on the dose determined by the Day 1 PK measurement, when that information becomes available.

e. Should the PK sub-analysis reveal dosing different from 0.1 mg BID, a subsequent protocol amendment will be required.

† An amended protocol will be implemented prior to enrollment of each subsequent age group and the dose rationale will be descried in an appendix.

Age Group to be used for analyses: Age Group 1: 12 to <18 years; Age Group 2: 2 to <12 years; Age Group 3: 28 days to <2 years; Age Group 4: Neonates (birth to ≤27 days).

1.3. Benefit & Risks of Apixaban

The following section reviews the potential benefits and risks of apixaban for subjects enrolled in this study.

1.3.1. Potential Benefits to Subjects

As demonstrated in a number of clinical studies, apixaban has potent, predictable and lasting anticoagulant activity and a predictable 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, limited potential for clinically significant 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 a venous thromboembolism, 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.

1.3.2. Potential Risks to Subjects

The primary safety risk for apixaban, as well as any anticoagulant, is undesired bleeding. Based on safety data obtained in the adult clinical program from over 70,000 subjects, approximately 40,000 of whom were treated with apixaban, and post-marketing experience from over 29 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),[20] it is interesting to learn that in patients undergoing invasive procedures while taking apixaban, the rates (treatment interrupted, treatment not interrupted) of post-procedural major bleeding (1.65%, 1.59%) and death (1.0%, 1.4 %) were low whether apixaban was interrupted or continued; whereas in patients taking warfarin, the rates of post-procedural major bleeding (1.26%, 3.04%) and death (0.5%, 2.0%) were at least 2-fold higher among those who continued warfarin versus those who interrupted treatment.[2]

1.3.2.1. Protection Against Risks

To minimize the risk of bleeding, subjects with active bleeding or high risk of bleeding (eg, central nervous system tumors) as well as intracranial bleed including recent intraventricular hemorrhage 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 External Data Monitoring Committee (EDMC) which also review the data from the other pediatric apixaban studies for a complete safety signal. The EDMC will have the responsibility to review the incidence of bleeding and thromboembolic events and will be provided with reports of SAEs on a regular basis. The EDMC may recommend modification or suspension of the trial for safety reasons.

In addition to EDMC 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 EDMC, 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. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- Primary: To assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

- Secondary: To evaluate apixaban PK and anti-FXa activity in pediatric subjects requiring anticoagulation for the treatment of a VTE.

2.2. Endpoints

- **Primary Safety:** The composite of major and clinically relevant non-major bleeding.

- **Primary Efficacy:** A composite of: (i) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism and (ii) VTE-related mortality.

Secondary:

- All cause death.

- VTE related mortality.

- Index VTE status (eg, unchanged, regression, or resolution).

- Stroke.

- New or recurrent symptomatic or asymptomatic DVT.

- New or recurrent symptomatic or asymptomatic PE.

- VTEs, other than DVT or PE (ie, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis).

- Major bleeding.
- Clinically relevant non-major bleeding.
- Minor bleeding.
- Apixaban concentrations.
- Anti-FXa activity.

This protocol will use an independent Endpoint Adjudication Committee (EAC) wherein adjudication of disease-related efficacy and safety endpoints will be performed. For those Serious Adverse Events (SAEs) that are handled as disease-related efficacy endpoints, the Endpoint Adjudication Committee, in coordination with the External Data Monitoring Committee (EDMC), is responsible for ongoing analysis of these outcomes and for informing the sponsor of recommendations made (eg, to continue the study or to stop the study).

3. STUDY DESIGN

Treatment assignment will not be blinded. Up to 250 subjects will be randomized into the trial using a ratio of 2 to 1 to apixaban or SOC, respectively. A goal of 30 or more subjects will be randomized into each of the following three age groups to be used for analysis: (1) 12 to <18 years; (2) 2 to <12 years; (3) 28 days to <2 years; For age group 4, neonates (birth to ≤27 days), the sample size may be adjusted based on a PK sub-analysis that will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. The number of neonates on apixaban will not exceed 20 subjects. Enrollment caps may be used to manage enrollment per age group. Randomization will be stratified by age group. Enrollment will begin with the oldest age group. As of May 2019, enrollment to Age Groups 1 and 2 was completed and as of December 2020, enrollment to Age Group 3 (28 days to <2 years of age) was completed. Enrollment is now focused on the youngest age group, Group 4 (neonates, birth to ≤27 days with a minimum weight of ≥2.6 kg). Enrollment may be capped in any age cohort once adequate numbers are reached to fulfill the objectives of this study. Subjects 28 days of age or older may receive up to 14 days of standard anticoagulant treatment prior to randomization. For the study's neonate PK cohort, subjects ≤27 days of age, who will have been treated with standard of care therapies for 5 to 14 days prior to randomization, the dose will be targeted to achieve an exposure similar to 5 mg twice daily in adults. For the study's neonate post-PK cohort, (ie, those neonates recruited after the PK sub-analysis is completed), which may be treated with standard of care therapies for up to 14 days prior to randomization, the dose will be targeted to achieve an exposure similar to 10 mg twice daily for the first week, and 5 mg twice daily thereafter in adults.

Subjects 2 years of age or older, randomized to the apixaban arm will receive open-label apixaban for 12 weeks.

Neonates (birth to ≤27 days) and children 28 days to <2 years of age may receive open-label apixaban for 6 to 12 weeks, a duration consistent with the ACCP and ASH guidelines and clinical recommendation. Subjects randomized to the SOC arm will receive a dosing regimen of anticoagulation treatment based on usual and customary care per local practices and that will be aligned with the current, internationally recognized ACCP and ASH guidelines, or equivalent, for at least 12 weeks. Neonates (birth to ≤27 days) and children 28 days to <2 years of age may receive SOC for 6 to 12 weeks. SOC will be limited to heparin in subjects <2 years old (UFH or LMWH). Monitoring of SOC will be based on usual and customary care per local practices and should be aligned with the current guidelines. The remaining neonates (birth to ≤27 days) will be assigned and treated with apixaban only.

Subjects will be monitored for laboratory safety parameters. Monitoring will take place at the Day 1 and Day 42 visits and whenever clinically indicated.

The initial neonates treated with apixaban, and other neonates subsequently recruited prior to the completion of the neonate PK sub-analysis, will have three (3) PK measurements obtained during their first day of treatment. All apixaban treated subjects will have pre- and post-dose blood samples for peak and trough apixaban concentrations (PK) and anti-FXa activity levels (PD) at the Day 14 visit. If possible, PK samples for apixaban may be obtained within 24 hours of a major bleeding or a thrombotic event along with the time of the last dose prior to the event.

Radiologic imaging will be performed, and adjudicated, to confirm the index event (ie, primary diagnosis of thromboembolic event which will be treated with apixaban or SOC in this study). For subjects 2 years of age or older, in addition to the radiologic images obtained to confirm the index event, new radiologic images of the clot will be obtained at approximately the mid-point and end of treatment (EOT) visits. For subjects 28 days to <2 years of age and neonates (birth to ≤27 days of age) imaging should be performed at the EOT. All of the aforementioned imaging will be adjudicated.

Additional imaging assessments can be performed at the discretion of the Investigator, at any time during the study. Radiologic images that require sedation and/or radiation at the Day 42 or Day 84 (EOT) visits are not required and may be omitted, if not medically necessary. The reason for omitting images should be clearly documented in the appropriate Case Report Form (CRF). In addition, when medically appropriate, new radiologic images will be obtained if recurrent VTE is suspected. All assessments obtained in the evaluation of symptomatic or asymptomatic recurrent VTEs, performed after randomization, will be adjudicated. Further monitoring of thrombus status via radiologic images may be conducted per usual and customary practice.

Palatability of the apixaban oral solution, the apixaban 0.5-mg tablets and apixaban 0.1 mg sprinkle capsules will be assessed at the Day 14 study visit.

This study will be monitored by an EDMC. Stopping rules for this study will be developed a priori in collaboration with the EDMC. In addition, the EDMC will use their clinical and statistical judgment to recommend that the study proceed, be modified, or be terminated early.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Children from birth to <18 years of age with a minimum weight of 2.6 kg at the time of randomization.

    - An approved amended protocol will be implemented prior to enrollment of each subsequent age group.

    - Neonates are defined as infants from birth up to ≤27 days of life. For pre-term infants born between 34 and <37 weeks gestation, investigators have the option to define the 27 day neonatal period starting from the actual date of birth (post-natal age) or may choose to define the 27 day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reaches 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4. "Gestational age" is the time elapsed between the first day of the last normal menstrual period and the day of delivery. Neonates or infants born prematurely at <34 weeks' gestation are excluded from this study until the age of ≥6 months of life. Gestational age will only be taken into consideration for eligibility up to 6 months of age.

2. Presence of an index VTE which is confirmed by imaging. Index VTE include, but are not limited to, deep vein thrombosis, pulmonary embolus, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related thrombosis, and splanchnic thrombosis. **In Germany only**, cerebral sinovenous thrombosis will be excluded.

3. Intention to manage the index VTE with anticoagulation treatment for at least 12 weeks or intention to manage the index VTE with anticoagulation treatment in neonates (birth to ≤27 days) and children 28 days to <2 years of age for 6 to 12 weeks.

4. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study. Depending on local regulations, whenever the minor is able to give assent, the minor's assent must also be obtained.

5. Subjects/legally acceptable representatives who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective method of contraception throughout the study and for at least 33 days (5 half-lives plus 30 days) after the last dose of assigned treatment.

7. Subjects able to tolerate oral feeding, nasogastric (NG), gastric (G) feeding and are currently tolerating enteric medications, as per investigator's judgement.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Anticoagulant treatment for the index VTE for greater than 14 days prior to randomization. Neonates that are enrolled into the PK cohort must be on a minimum of 5 days and a maximum of 14 days SOC (eg, heparins or DTIs) anticoagulation prior to randomization. Neonates that are enrolled into the post PK cohort may receive SOC anticoagulation for up to 14 days prior to randomization.

2. Cerebral sinovenous thrombosis **(in Germany only)**.

3. Thrombectomy, thrombolytic therapy, or insertion of a caval filter to treat the index VTE.

4. A mechanical heart valve.

5. Active bleeding or high risk of bleeding (eg, central nervous system (CNS) tumors) at the time of randomization.

6. Intracranial bleed, including intraventricular hemorrhage, within 3 months prior to randomization.

7. Abnormal baseline liver function (ALT >3 x upper limit of normal (ULN) or conjugated bilirubin >2 x ULN) at randomization.

8. At the time of randomization, inadequate renal function as defined in Section 7.3.2. Estimated Glomerular Filtration Rate Assessment.

9. Platelet count $<50\times10^9$ per L at randomization.

10. At the time of randomization, uncontrolled severe hypertension as defined in Section 7.1 Physical Examination.

11. At the time of randomization, use of prohibited concomitant medication as listed for apixaban in Section 5.5 Concomitant Medication.

12. Known allergy to apixaban or any of the other ingredients in the apixaban formulation, or hypersensitivity to any of the components of the comparators.

13. Female subjects who are either pregnant or breastfeeding a child.

14. Geographically unavailable for follow-up.

15. Family members who are either investigational site staff members directly involved in the conduct of this trial or site staff members otherwise supervised by the Investigator. Family members who are Pfizer or Bristol Myers Squibb (BMS) employees directly involved in the conduct of this trial.

16. Taking an investigational drug in other studies within 30 days before the first dose of apixaban and/or during study participation. N.B. using marketed medications commonly used in usual and customary practice, though not labeled for use in children, is acceptable.

17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

19. Unable to take oral or enteric medication via the NG or G tube.

20. Known inherited or acquired antiphospholipid syndrome (APS).

21. Known inherited bleeding disorder or coagulopathy with increased bleeding risk (eg, hemophilia, von Willebrand disease, etc.)

4.3. Life Style Guidelines

All female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active and at risk for pregnancy, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 33 days (5 half-lives plus 30 days) after the last dose of investigational product, which includes SOC. The investigator, or his/her designee, in consultation with the subject, will select or confirm that the subject has selected the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly

effective contraception consistently and correctly according to the Schedule of Activities (SOA) and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject/legally acceptable representative directly and if

a subjects/legally acceptable representative calls that number he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

Subjects ≥2 years of age will receive open-label apixaban (Arm 1) or Standard of Care (Arm 2) for at least 12 weeks. Neonates (birth to ≤27 days) and children 28 days to <2 years of age will be treated for 6 to 12 weeks.

Subjects randomized to Arm 2 will receive a dose and dosing regimen of anticoagulation treatment based on usual and customary care per local practices. Monitoring of SOC will be based on usual and customary care per local practices and should be aligned with current local guidelines.

Table 3. Study Treatments

Arm	Treatment	Dose	Route	Duration
1	Apixaban	Dosing based on age and body weight (Table 2)	Oral	12 Weeks (6 to 12 Weeks)[a]
2	Vitamin K antagonist (VKA)	Standard of care per local prescribing practices/guidelines**	Oral	12 Weeks (6 to 12 Weeks)[a]
	Low molecular weight heparin (LMWH)	Standard of care per local prescribing practices/guidelines	Subcutaneous	12 Weeks alone (6 to 12 Weeks alone)[a] or until INR is ≥2 with a VKA
	Unfractionated heparin (UFH)	Standard of care per local prescribing practices/guidelines	Intravenous	12 Weeks alone (6 to 12 Weeks alone)[a] or until INR is ≥2 with a VKA

[a.] Treatment duration in subjects 28 days to <2 years of age will be 6 to 12 weeks and limited to heparins (UFH or LMWH). The neonate subjects (birth to ≤ 27 days) will be assigned and treated with apixaban only.

5.1. Allocation to Treatment

Treatment assignment will not be blinded. Up to 250 subjects will be randomized into the trial using a ratio of 2 to 1 to apixaban or SOC, respectively. A goal of 30 or more subjects will be randomized into each of the following three age groups: (1) 12 to <18 years; (2) 2 to <12 years; (3) 28 days to <2 years. For the age group 4, neonates (birth to ≤27 days), the sample size may be adjusted based on a PK sub-analysis that will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. The number of neonates on apixaban will not exceed 20 subjects. The remaining neonates (birth to ≤27 days) will be assigned and treated with apixaban only.

Neonates are defined as infants from birth up to ≤27 days of life. For pre-term infants born between 34 and <37 weeks gestation, investigators have the option to define the 27 day neonatal period starting from the actual date of birth (post-natal age) or may choose to define the 27 day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reaches 37 weeks and enroll the infant no more than 27 days thereafter into

Cohort 4. "Gestational age" is the time elapsed between the first day of the last normal menstrual period and the day of delivery. Neonates or infants born prematurely at <34 weeks' gestation are excluded from this study until the age of ≥6 months of life. Gestational age will only be taken into consideration for eligibility up to 6 months of age. Enrollment caps may be used to manage enrollment per age group without a needed amendment. Enrollment will begin with the oldest age group. An approved amended protocol will be implemented prior to enrollment of each subsequent age group.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Apixaban will be provided as 5 mg tablets, or 0.5 mg tablets, 0.1 mg sprinkle capsules, or as 0.4 mg/mL solution for oral administration. Apixaban oral solution must be used only in children ≥5 years of age because the daily intake of [redacted] would exceed the threshold specified in a 2014 draft EMA guideline for children <5 years of age.[10,11] The apixaban 5 mg tablets, 0.5-mg tablets, and 0.1 mg sprinkle capsules will be packaged in [redacted] and labeled according to local regulatory requirements. Children <5 years of age, at least 4 kg to <35 kg weight, and randomized to the apixaban arm should only receive the 0.5-mg tablet or 0.1 mg sprinkle capsule formulation in accordance with the dosing instructions and regulatory requirements referenced within the protocol.

Apixaban 0.4 mg/mL oral solution is intended to be used only in children ≥5 years of age and will be provided in [redacted] labeled according to local regulatory requirements.

In addition to 0.5 mg strength, the 0.1 mg sprinkle capsule was developed for pediatric subjects. [redacted]

5.2.2. Preparation and Dispensing

Every effort should be made to keep a subject on the same formulation and dosing regimen (tablet, oral solution or sprinkle capsule formulation) for the duration of the study. However, a change in formulation (if permissible per age and body weight restrictions for the available apixaban formulations) will be permitted during the study in order to retain the subject in the study.

Subjects who were originally randomized and dosed according to a weight-based (mg/kg) regimen presented in Table 2 (Amendment 3) and who are still on investigational product at the time of Amendment 4 approval, will continue on this weight-based regimen. Subjects randomized to receive apixaban after implementation of Amendment 4 of the protocol will follow the fixed-dose, body weight-tiered regimen provided Table 2 using the appropriate formulation. If a change in formulation (ie, change from oral solution to 0.5-mg tablets) is necessary for a subject randomized and dosed under Amendment 3, then the subject will need to switch from mg/kg dosing to the tiered fixed-dose regimen based on the subject's

weight and age. This should only be done if the change in formulation is needed to retain the subject in this trial.

Randomization should occur on Day 1. The apixaban dose will be provided by the central randomization and drug assignment system. Preparation and dispensation of the initial apixaban drug supply, assigned during randomization, should occur on Day 1. Preparation of any subsequent apixaban drug supply may occur prior to or at the time of a site visit. Dispensation of any subsequent apixaban drug supply will occur at the time of a site visit.

Once the subject is randomized to the apixaban arm by the central randomization and drug assignment system, the site will dispense the assigned [redacted] of investigational product during the Day 1, Day 14 and Day 42 visits. If the subject continues in the extension phase on apixaban, investigational product will be dispensed at Day 84 and Day 126. The total number of [redacted] dispensed at each visit will be determined based on the dose required for each individual subject. A qualified staff member will dispense the investigational product [via unique container numbers] in the [redacted] provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the original [redacted] provided throughout the course of dosing and return all [redacted] and remaining investigational product and supplies to the site at the next study visit.

Apixaban

5 mg tablets will be dispensed for subjects ≥35 kg, 0.5-mg tablets will be dispensed for subjects ≥5 kg to <35 kg, and 0.1 mg sprinkle capsules for subjects <5 kg.

Apixaban 0.5 mg tablets and 0.1 mg sprinkle capsules may be used in subjects 28 days to <2 years of age with a minimum of 4 kg body weight. Neonates will only be administered 0.1 mg sprinkle capsules, with a minimum of 2.6 kg body weight. Apixaban oral solution may only be used in children ≥5 years of age. No special precautions are required for the preparation and handling of apixaban. oral solution or tablet formulations.

Dispensing and subject/caregiver training on and confirmed understanding of administration and dosing will be done by a qualified staff member. The subject/legally acceptable representative should be instructed to maintain the product in the [redacted] provided throughout the course of dosing and return all (used and unused) [redacted] to the site at the next study visit.

Apixaban 0.5 mg tablets may be prepared in [redacted] (ie, [redacted]) or [redacted] (ie, [redacted]) mediums. Apixaban 0.1 mg sprinkle capsules may only be prepared in [redacted] (ie, [redacted]) mediums. Refer to the Investigational Product (IP) Manual and the separate instructions provided for complete details regarding the preparation and administration of each apixaban formulation.

Standard of Care

Special precautions required for handling standard of care should be followed as indicated in the label for that specific product.

Except where prohibited by local regulations, sites are responsible for providing standard of care (both drug and dosing instructions) for subjects enrolled into the standard of care arm. For subjects 28 days to <2 years of age, SOC will be limited to heparins (UFH or LMWH). The remaining neonate subjects (birth to ≤27 days) will be assigned and treated with apixaban only.

5.2.3. Administration

Apixaban

The apixaban dose will be provided by the central randomization and drug assignment system. Appropriate formulations will be provided to those subjects based on age and weight requirements. Multiple apixaban 0.5 mg tablets or 0.1 mg sprinkle capsules may be required to deliver the prescribed dose. Refer to the pharmacy manual for additional information regarding dosing, dosage forms, and administration.

It is recommended that prior to the administration of the first dose of apixaban:

- ≥2 hours have passed since the last dose of UFH;
- ≥6 hours have passed since the last dose of LMWH labeled for twice daily administration;
- ≥12 hours have passed since the last dose of fondaparinux or LMWH labeled for once daily administration; or
- the INR ≤2 for subjects receiving a VKA.

First Dose Administration of Apixaban

Day 1 will be set at the time of randomization. For subjects who are currently on another anticoagulation therapy and need to wait for their first dose of apixaban due to timelines, the first dose of apixaban should be administered at the clinic visit.

At Home Administration of Apixaban (First Dose)

For those who cannot receive their first dose of apixaban during clinic hours on Day 1, the qualified site member shall dispense the investigational product and demonstrate the appropriate preparation and administration method of the oral solution or tablet formulations for dosing at home. The site will also need to update the subject's dosing diary to reflect that the first dose of apixaban was administered at home. First dose administration at home will not be considered a protocol deviation. Administration instructions shall be given to the caregiver and/or subject depending on the age of the subject. An appropriately qualified site staff member shall dispense the investigational product along with the appropriate preparation and administration instructions to the subject and/or caregiver. The site shall also confirm that the subject and/or caregiver is able to demonstrate proper preparation as well as administration [redacted] of apixaban to the subject while

at the clinic, and record confirmation of this in the site's source documents. Dosing should continue twice daily (BID), approximately 12 hours apart, for 7 days (eg, 14 total doses). The dose will be decreased for Day 8 and onwards as described in Table 2. Subjects/caregivers shall be educated on changes in dosing for Day 8 and beyond. Sites shall contact the subject/caregiver on Day 7 to educate and remind them of the dosing changes. This interaction shall be documented in the source documentation.

Apixaban administration:

Apixaban can be administered by mouth (PO) or via a nasogastric tube or gastrostomy tube followed with or without food approximately 12 hours apart.

Tablets: Apixaban 5-mg tablets may be [redacted] and immediately administered orally. Alternatively, apixaban 5-mg tablets may be [redacted] and immediately delivered through a nasogastric tube. The apixaban 0.5- mg tablet may be mixed with [redacted] and promptly administered orally. Preparation and administration instructions for the apixaban 0.5 mg tablets will be provided and will include administration instructions for those children who cannot [redacted] tablets or take [redacted].

Oral solution: The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor and only in children ≥5 years of age (see Section 5.2.1). Administration of the apixaban oral solution (0.4 mg/ml) via nasogastric tube or gastrostomy tube is acceptable as is the use of either [redacted] as flush media for the nasogastric or gastrostomy tubes. When administering via nasogastric tube or gastrostomy tube, coadministration of the apixaban oral solution (0.4 mg/ml) with an enteral meal is also acceptable.

Sprinkle Capsule: The apixaban 0.1 mg sprinkle capsule may only be dissolved in water or formula and promptly administered via orally, NG or G tube. Preparation and administration instructions for the apixaban 0.1 mg sprinkle capsules will be provided separately.

As data are obtained for the other age groups in the CV185118 study, the modeling and simulation results will be updated and used to support dosing recommendations for the neonate group. An approved amended protocol will be implemented prior to enrollment of each subsequent age group.

Vomiting: If a subject vomits within 30 minutes of ingestion of the study drug, the full dose of study drug should be repeated. If a subject vomits 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. If the subject vomits or spits up repeatedly, the caregiver should contact the Investigator.

Apixaban treatment beyond the Day 84 visit (Extension Phase): For subjects who require additional anticoagulation for the treatment of their index event, were compliant with the administration of apixaban, and completed all study visits and activities, apixaban will be made available for 6 or 12 additional weeks. For subjects who require long term anticoagulation beyond the 12 additional weeks (ie, Day 84 visit plus 12 additional weeks), a switch to SOC should be made after the end of treatment (Day 84) visit but no later than the Day 168 visit. Subjects who were randomized to SOC on Day 1 may not continue in this study beyond Day 84.

For subjects who require 6 additional weeks of anticoagulation, the Day 28 and 42 visits will be repeated at Days 105 and 126, respectively, followed by the 35-day follow up visit. An EOT page will be completed when the subject has finished the 6-week or 12-week additional weeks. Investigational product will be dispensed on Day 84 for 6 additional weeks of treatment. For subjects who require 12 additional weeks of anticoagulation, the Day 28 and 42 visits will be repeated at Days 105 and 126, respectively, and the Day 63 and 84 visits will be repeated at Days 147 and 168, respectively, followed by the 35-day follow up visit. Subjects receiving 12 additional weeks of investigational product will return on Day 126 and the remaining study medication should be dispensed at this visit in accordance with the procedures outlined for Day 42 (Section 6.4).

5.2.4. Compliance

Subjects should not be discontinued from the trial based solely on compliance.

To facilitate investigational product (IP) compliance, sites where permissible may offer caregivers the option to work with a designated trained home healthcare worker or trained site staff for investigational product administration at home. This is not required for the study. Trained designated home healthcare workers provide additional guidance for dosing apixaban in children for the first dose at home or throughout the duration of the study if the caregiver and Investigator feels this would be beneficial. Sites should appropriately document when a home healthcare service is used for subject investigational product administration as directed by the Sponsor. For the neonate PK cohort, if the first dose is administered at home, the trained home healthcare worker or trained site staff will draw, collect and appropriately transport back to site the Day 1 PK collection procedures (as described in Section 7.4.1 Sampling Time Points and Section 7.2.2 for special requirements when a dried blood spot blood collection method is used).

Apixaban

Compliance based on pill count and volume of solution remaining will be performed by a qualified site staff member at each scheduled visit for subjects receiving apixaban. Compliance will be reinforced at each study visit and the importance should be reiterated at each telephone visit. Subjects must maintain adequate compliance with the investigational product regimen. If a discrepancy of more than 20% of doses exists since the last scheduled visit, the site staff should re-instruct the subject/caregiver on the importance of compliance with medical treatment for their disease and on the dosing regimen.

Standard of Care

Compliance will be managed as usual and customary for each individual subject at that site. Compliance will be reinforced at each study visit. If a significant discrepancy with compliance exists since the last scheduled visit, the site staff should re-instruct the subject/legal guardian on the importance of compliance with medical treatment for their disease and on the dosing regimen.

5.3. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label.

Storage conditions stated in the Single Reference Safety Document (SRSD) will be superseded by the label storage.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported to the Sponsor or Sponsor's delegate upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined in required temperature conditions and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects/legally acceptable representatives on the storage requirements for take home medications including how to report temperature excursions.

Drug storage for standard of care treatments will be based on local practice and as indicated in the drug label.

5.4. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP. All dispensed and returned IP will be accounted for using a drug accountability form/record.

All [redacted] of apixaban (used and unused) must be returned to the investigator by the subject/caregiver.

The sponsor or designee will provide guidance on the return to the sponsor or the destruction of unused investigational product.

Drug accountability for standard of care treatments shall be performed according to local site procedures.

5.5. Concomitant Medication(s)

Apixaban

The following medications or therapies are prohibited during the treatment period for subjects on apixaban:

- Concomitant systemic treatment with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, and ritonavir.
    - Note that fluconazole, topical azole antifungal agents, trimethoprim-sulfamethoxazole, H2-antagonists, and proton pump inhibitors are acceptable and permitted.
- Concomitant systemic treatment with strong inducers of both cytochrome CYP3A4 and P-gp, such as phenobarbital, phenytoin, fosphenytoin, rifabutin, rifampin, carbamazepine, St. John's wort.
- Aspirin >165 mg per day and other antiplatelet therapy such as thienopyridines (eg, clopidogrel, ticlopidine).
- Other antithrombotic agents (eg, UFH, LMWH, direct thrombin inhibitors, factor Xa inhibitors, fondaparinux).
    - Note that heparin flushes to maintain central venous access device (CVAD) patency and local tissue plasminogen activator to restore CVAD patency are permitted.
- GP IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban).

- Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid.

If treatment with a prohibited agent becomes necessary, investigational product should be temporarily interrupted, and restarted as soon as possible following discontinuation of the prohibited medication or therapy.

6. STUDY PROCEDURES

6.1. Screening (Day -14 through Day 1)

The Investigator or designee will:

- Obtain written informed consent. Obtain assent where appropriate (See Section 12.3).
- Determine if the subject meets the inclusion and exclusion criteria.
- Obtain relevant medical history.
- Perform physical examination including:
  - Measure height/body length;
  - Measure weight;
  - Measure vital signs.
- Conduct pregnancy test (women of childbearing potential (WOCBP) only).
- Provide education and document use of contraception in accordance with Section 4.3.
- Assess prior medication use (includes medication administered within the last 30 days).
- Assess only serious adverse events that occur after obtaining written informed consent.

6.2. Study Period

6.2.1. Day 1 (Day 1 Visit may Coincide with the Screening Visit)

The Investigator or designee will:

- Determine if the subject continues to meet the inclusion and exclusion criteria.

- Obtain blood samples for central clinical laboratory hematology and blood chemistry tests. To minimize blood sampling collected subjects <2 years of age may use local laboratory results for evaluation of hematology and blood chemistry.
- Conduct pregnancy test (WOCBP only).
- Assess prior medication use.
- Randomize the subject using the central randomization and drug assignment system interactive response technology (IRT).
    - For subjects on anticoagulant treatment for the index VTE prior to randomization, Day 1 will be set at the time of randomization. Subjects may be treated with SOC up to 14 days prior to randomization.
- Prepare and dispense study treatment.
- Administer the first dose of investigational product and provide education on dose preparation and administration instructions for future administration (eg, home administration, self or caregiver/guardian administration). The site should properly record those appropriate instructions that were provided to the caregiver/subject as source documentation. Refer to Section 5.2.3.
    - Subjects on another anticoagulation therapy should wait according to timelines set forth in Section 5.2.3 before receiving the first apixaban dose.
    - First dose should be administered during the clinic visit unless the subject is receiving the first dose of apixaban at home:
        - If dosing on Day 1 is given at home, the trained home healthcare worker or trained site staff will must dispense investigational product, and document that the appropriate preparation and administration instructions were provided to the caregiver/subject depending on the subject's age.
    - If a subject receives the first dose at home, instruct the subject/caregiver to document this in the subject's dosing diary. This is not a protocol deviation.
    - Dosing should continue twice daily (BID) for 7 days (eg, 14 doses). Dosing for Day 8 onward should be in accordance with and be reviewed with the subject/caregiver depending on the subject's age. Sites may contact the subject/caregiver on Day 7 to reiterate the change in dosing instructions given Day 8 onward in this study. This should be documented in the source.
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Provide the required documentation for the index event to the adjudication committee as soon as possible during the period that extends from Day 1 to Day 14.

- Assess all adverse events.

- Three blood samples for PK assessment will be obtained as described in Section 7.4.1 Sampling Time Points, only for the neonates recruited into the study, prior to the completion of the neonate PK sub-analysis. If a dose change is required, based on the PK analysis, the procedures for making a dose change will be described in a separate reference document.

6.2.2. Day 14 (Visit Window: Day 7 to Day 14)

The Investigator or designee will:

- Perform targeted physical examination as described in Section 7.1 Physical Examination. For subjects in the neonate cohort, weight can be rechecked prior to Day 14, at Day 14, or a subsequent visit when the subject reaches 28 days of age, for the purposes of determining whether the subject's dose should be modified.

    - In addition, if there is a 20% change in weight for any subjects less than 2 years old, the investigator may contact the study Sponsor to discuss a possible change in dosing regimen.

- Conduct pregnancy test (WOCBP only).

- Assess concomitant medication use.

- Collect used and unused apixaban containers dispensed previously.

- Assess compliance with study treatment.

- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).

- Dispense study treatment.

- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Unless provided previously, please provide the required documentation for the index event to the adjudication committee as soon as possible during the period that extends from Day 1 to Day 14.

- Conduct palatability assessment with subjects taking apixaban.

- Assess adverse events.

- Obtain blood samples for PK/PD assessment from subjects receiving apixaban as described in Section 7.4.1 Sampling Time Points.

6.2.3. Day 28 (Visit Window: Day 21 to Day 35)

The Investigator or designee will:

- Conduct the visit by telephone or on site.
- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.
- Assess adverse events.

6.2.4. Day 42 (Visit Window: Day 35 to Day 49)

The Investigator or designee will:

- Perform targeted physical examination as described in Section 7.1 Physical Examination. If there is a 20% change in weight for subjects less than 2 years old, the investigator may contact the study Sponsor to discuss a possible change in dosing regimen.
- Conduct pregnancy test (WOCBP only).
- Obtain blood samples for central clinical laboratory hematology and blood chemistry tests. For subjects <2 years of age a local lab test may be completed to fulfill this assessment and noted in the appropriate CRF.
- Assess concomitant medication use.
- Collect used and unused apixaban containers dispensed previously to subjects.
- Assess compliance with investigational product.
- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).
- Dispense investigational product.
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Reassess the index event and all areas around the index event that were imaged initially based on the clinical assessment to account for the presence of any new asymptomatic clots. Provide documentation for this reassessment to the adjudication committee as soon as possible. Images and documentation to support this reassessment may be obtained anytime between Day 28 and Day 56 (Day 42 ± 14 days). Radiologic images that require sedation or radiation at the Day 42 visits are not required and may be omitted, if not medically necessary.

- Assess all adverse events.

- If pre and/or post-dose blood samples were not drawn on Day 14 for PK/PD assessment, then obtain the missing sample(s) from subjects receiving apixaban as described in Section 7.4.1 Sampling Time Points. Otherwise, samples are not required at the Day 42 visit.

- For subjects up to <2 years of age receiving only 6 weeks of study treatment, Day 42 and Day 84 (EOT) procedures should be combined.

6.2.5. Day 63 (Visit Window: Day 56 to Day 70)

The Investigator or designee will:

- Conduct the visit by telephone or on site.

- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).

- Assess adverse events.

6.2.6. Day 84 or End of Treatment (Visit Window: Day 77 to Day 91)

The Investigator or designee will:

- Perform targeted physical examination as described in Section 7.1 Physical Examination.

- Assess concomitant medication use.

- Collect used and unused apixaban containers dispensed previously.

- Assess compliance with study treatment.

- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).

- Reassess the index event and all areas around the index event that were imaged initially based on the clinical assessment to account for the presence of any new asymptomatic thrombi. Provide documentation for this reassessment to the adjudication committee as soon as possible. Radiologic images that require sedation or radiation at the Day 84 (EOT) visits are not required and may be omitted, if not medically necessary.

- Assess all adverse events.

- For subjects less than 2 years of age receiving only 6 weeks of study treatment, Day 42 and Day 84 (EOT) procedures should be combined.

6.3. Follow-up Visit (35 Days ±5 After the EOT Visit) (Visit Window: EOT +30 to EOT +40)

The Investigator or designee will:

- Conduct the visit by telephone or on site.

- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Assess adverse events by telephone contact or site visit.

6.4. Extension Phase (Only applicable for apixaban treated subjects in age cohorts 1, 2, and 3, who have completed 12 weeks of treatment) (Visit Window Day 105 Through 168)

Apixaban treated subjects 28 days of age or older, who have completed 12 weeks of treatment, may continue treatment beyond Day 84 for 6 or 12 additional weeks in the Extension Phase. End of Treatment activities should be completed at Day 126 or Day 168. The following procedures should be completed at the described visits below:

Day 105 ±7:

The Investigator or designee will:

- Conduct the visit by telephone or on site.

- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).

- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Assess adverse events.

Day 126 ±7:

The Investigator or designee will:

- Perform targeted physical examination as described in Section 7.1 Physical Examination.
- Conduct pregnancy test (WOCBP only).
- Obtain blood samples for central clinical laboratory hematology and blood chemistry tests. To minimize blood sampling collected subjects <2 years of age may use local laboratory results for evaluation of hematology and blood chemistry.
- Assess concomitant medication use.
- Collect used and unused apixaban containers dispensed previously to subjects.
- Assess compliance with study treatment.
- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).
- Dispense study treatment if subject is continuing in 12-week extension phase (to Day 168).
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.
- Reassess the index event and all areas around the index event that were imaged initially based on the clinical assessment to account for the presence of any new asymptomatic clots. Provide documentation for this reassessment to the adjudication committee as soon as possible. Radiologic images that require sedation or radiation at the Day 126 visits are not required and may be omitted, if not medically necessary.
- Assess adverse events.

Day 147 ±7:

The Investigator or designee will:

- Conduct the visit by telephone or on site.
- Confirm subject/caregiver understanding of dosing instructions (noted in source documentation).
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.

- Assess adverse events.

Day 168 ±7:

The Investigator or designee will:

- Perform targeted physical examination as described in Section 7.1 Physical Examination.
- Conduct pregnancy test (WOCBP only).
- Obtain blood samples for central clinical laboratory hematology and blood chemistry tests. To minimize blood sampling collected subjects <2 years of age may use local laboratory results for evaluation of hematology and blood chemistry.
- Assess concomitant medication use.
- Collect used and unused apixaban containers dispensed previously.
- Assess compliance with study treatment.
- Confirm and document use of contraception, if required according to Section 4.3 Life Style Guidelines.
- Reassess the index event and all areas around the index event that were imaged initially based on the clinical assessment to account for the presence of any new asymptomatic thrombi. Provide documentation for this reassessment to the adjudication committee as soon as possible. Radiologic images that require sedation or radiation at the Day 168 (EOT) visits are not required and may be omitted, if not medically necessary.
- Assess all adverse events.

6.5. Follow-up Visit (35 Days ±5 After the EOT Visit) (Visit Window: EOT +30 to EOT +40)

- See Section 6.3.

6.6. Temporary Treatment Interruptions

During the course of the study, situations might occur in which the investigator considers a temporary interruption of study drug treatment to be indicated (eg, lumbar puncture, catheter replacement, scheduled surgical procedure, thrombocytopenia, or elevated liver function tests). The treating physician should be made aware that when apixaban is administered at the protocol-specified doses, routine coagulation tests such as INR/prothrombin time (PT) and aPTT are relatively insensitive measures of activity and therefore may be unsuitable for monitoring. Dose interruptions for selected events are described in Table 4. For treatment interruptions ≥24 consecutive hours, the period of interruption should be noted, and the

investigator should document the following on the case report form (CRF): time of discontinuation and resumption of therapy, and the reason for discontinuation. If the treatment interruption is due to reasons other than the ones described in Table 4, a protocol deviation should be recorded. An adverse event (AE)/SAE should be reported, if applicable, and relatedness of the AE(s) will be determined by the investigator. For an individual subject, dose interruptions and treatment discontinuation may be more conservative than indicated below in Table 4, based on the clinical judgment of the investigator. Note that discontinuation of subjects from treatment is addressed in Section 6.7.

Table 4. Temporary Dose Interruptions for Apixaban

Event	Apixaban
Lumbar punctures (LPs)	Apixaban should be held for at least 24 hours prior to any planned LP and will resume no earlier than 12 hours after the procedure.
Scheduled surgical procedures	Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. If a subject participating in the study requires an elective procedure or surgery, the following considerations should be taken into account: 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 (eg, at least 24 hours) prior to the procedure to minimize the risk of anticoagulant-related bleeding. The treating physician should be made aware that when apixaban is administered at the protocol-specified doses, routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of anticoagulation activity and are unsuitable for monitoring the anticoagulation effect of apixaban. The subject will be re-started on discontinued study medication once hemostasis is secure and when, in the opinion of the investigator, it is safe to do so.
Thrombocytopenia. An AE/SAE should be reported if applicable	There is no evidence-based guidelines for anticoagulation therapy in relation to platelet counts. In the absence of any other coagulopathy, the following guidelines are recommended during the course of the study period: • Full-dose apixaban therapy for subjects with platelet count $\geq 50\times10^9$ per L. • Withhold apixaban for platelet count $<50\times10^9$ per L. Close monitoring of platelet count and careful watching for signs of bleeding are necessary.
Elevated liver function tests. An AE/SAE should be reported if applicable	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 (conjugated) bilirubin, alkaline phosphatase, GGT, CK as soon as possible (ie, within 3 days). If the repeat tests indicate: 1. ALT <5 x ULN and direct (conjugated) bilirubin ≤2 x ULN, study medication may **continue.**

Event	Apixaban
	2. ALT/AST ≥5 x ULN **AND/OR** the direct (conjugated) bilirubin is >2 x ULN, the study medication must be interrupted. The study medication must be interrupted if: • Clinical jaundice is present for 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 • 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 the 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 Medical Monitor and Study Director and perform the following: • PT, 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. Discontinuation of Subjects from Investigational Product

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's or guardian's decision to withdraw for any reason).
- Any clinical adverse event (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.
- Pregnancy.
- Termination of the study by Bristol-Myers Squibb (BMS)/Pfizer.
- Loss of ability to freely provide consent (subject or guardian) through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

- Thromboembolic event such as DVT, PE, cerebral sinovenous thrombosis or arterial thromboembolic event.

- For the neonate PK cohort, if a 90% prediction interval cannot be achieved with either 0.1 mg daily or 0.2 mg twice daily, the subject will be discontinued from apixaban.

In the case of pregnancy, the investigator must immediately notify the medical monitor of this event. Please refer to Section 8.4 for follow-up. The investigational product will be permanently discontinued in an appropriate manner.

Once any study-specified thromboembolic or any major bleeding event endpoint is met, every effort must be made to confirm a suspected thromboembolic or bleeding event. Management of any asymptomatic or symptomatic events will be according to the local standards of practice. If study medication is discontinued for a suspected thromboembolic event, alternative anticoagulant therapy may be initiated per the Investigator's discretion and standard of care.

All subjects who discontinue investigational product (ie, are off protocol therapy) irrespective of reason, should remain in the study and complete the EOT visit and Safety Follow Up Visit, as described in the Schedule of Activities. The reason for the discontinuation must be documented in the subject's medical records and a status page should be completed on the appropriate CRF page.

The only exception to this requirement is when a subject/guardian 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). The Medical Monitor and Study Director should be informed of these situations.

Subjects/legally acceptable representatives may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject/legally acceptable representative. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject/legally acceptable representative to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow up with the subject/legally acceptable representative regarding any unresolved adverse events (AEs).

If the subject/legally acceptable representative withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.8. 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 by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by 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, in order 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.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Physical Examination

Physical exam, including vital signs (heart rate, respiratory rate, and blood pressure) and physical measurements (height/body length and body weight) will be conducted at screening.

Since dosing will be based on body weight, minimal clothing should be worn during the body weight measurement.

Uncontrolled severe hypertension at randomization is an exclusion criterion and is defined as a systolic or diastolic blood pressure (BP) $\geq 99^{th}$ percentile plus 5 mmHg as defined by the National High Blood Pressure Education Program Working Group (NHBPEP) established guidelines for the definition of normal and elevated blood pressures in children in 1987 and

updated in 2004. These children require a prompt evaluation and immediate pharmacologic treatment [NHBPEP, 2004].[24]

Targeted physical examinations for evidence of bleeding will be performed at Day 14, 42, and 84 (EOT) visits and as clinically indicated.

7.2. Blood Volume Collection

7.2.1. For Subjects 28 Days of Age or Older

The current total maximum potential blood sampling volume for individual subjects (ie, ≥28 days of age, and ≥4 kg weight) in this study is approximately 16.7 mL (this would include the optional 6-12 week extension visit for apixaban subjects only) for subjects randomized to apixaban and 9.3 mL for subjects randomized to SOC. Maximum blood volumes will be based on the child's weight and in accordance with local thresholds. The actual collection times of blood sampling may change. INR may need to be repeated as per local site procedures for those subjects on standard of care (SOC). Additional blood samples may be taken for safety assessments at times specified by the Sponsor, provided the total volume taken during the study does not exceed 1% of the total blood volume (eg, 0.8 mL/kg) at a single instance and up to 3% (2.4 mL/kg) over a four-week period in accordance with the 2008 version of the EU guidance titled, 'Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population.'[9] Table 5 summarizes the total blood volume that may be collected from a subject who is randomized to either Apixaban or SOC.

7.2.2. For Neonates (≤27 days of age)

Given the low body weight of neonates, and their low absolute circulating blood volume, special attention must be paid to the amount of blood drawn for neonates. For the neonates recruited into the study, prior to the completion of the neonate PK sub-analysis, it is expected that the maximum blood volume for the 3 apixaban PK blood samples will be ≤3 mL total. To mitigate excessive blood loss for the purposes of PK blood sampling, dried blood spot PK samples may be acquired in lieu of direct venous phlebotomy. Dried blood spot (DBS) analysis has been developed as a blood volume preservation option for neonates (approximately 45 microliters of blood per DBS sample). If DBS is the method of choice, a hematocrit result must have been drawn and available from a local laboratory within 48-72 hours prior to the first PK sample timepoint (Day 1 for PK cohort, Day 14 for PK and post PK cohort). Further details of blood collection and processing will be provided to the site in a procedure manual. Additional blood samples may be taken for safety assessments at times specified by the Sponsor, provided the total volume taken during the study does not exceed 1% of the total blood volume (eg, 0.8 mL/kg) at a single instance and up to 3% (2.4 mL/kg) over a four-week period in accordance with the 2008 version of the EU guidance titled, 'Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population.'[9] Table 6 summarizes the total blood volume that may be collected from a subject who is randomized to either Apixaban or SOC.

Table 5. Blood Sampling (Screening to EOT)

						Optional Extension Phase[a]		
Procedure	Subjects	Screening[b]	Day 1	Day 14	Day 42	Day 126	Day 168	Comments
Local Safety Labs[d,e]	All Subjects	~1.0-4.0 mL[b]						Based on local site procedures
Central Safety Labs (Chemistry, Lipid, Hematology & Differential)	All Subjects		2.3 mL		2.3 mL	2.3 mL	2.3 mL	
Serial PK and anti-FXa activity[c]	Subjects taking apixaban			1.4 mL	1.4 mL			
Day 1 PK	Neonates only[f]		≤3 mL					
Total (Potential) Maximum Blood Volume (mL) – **APIXABAN**		***≤4 mL***[b]	***≤3 mL***	***1.4 mL***	***3.7 mL***	***2.3 mL***	***2.3 mL***	Total to Day 84; ≤12.1 mL Total with Extension: ≤16. 7 mL
Total (Potential) Maximum Blood Volume (mL) – **SOC**		***≤4 mL***[b]	***≤3 mL***		***2.3 mL***			Total: ≤9.3 mL

a. Day 126 and Day 168 are only applicable to those apixaban subjects who enter the optional 6-12 week extension phase.

b. To satisfy eligibility requirements, up to 4 mL of blood may be drawn within 7 days prior to randomization. These should be the most recent, local laboratory tests. Maximum blood volumes will be based on the child's weight and in accordance with local thresholds.

c. If possible, obtain within 24 hours of any major bleed or thrombotic event and record time of last dose prior to the event. If one or both samples are not drawn during the Day 14 visit, then the procedure should be repeated at the Day 42 visit to obtain the missing sample(s).

d. Lab tests include platelets, serum creatinine, ALT, conjugated bilirubin INR, pregnancy test. Pregnancy test will be collected in women of childbearing potential only.

e. INR may need to be repeated as per local site procedures for those subjects on standard of care (SOC).

f. Only for neonates recruited prior to completion of the neonate PK sub-analysis.

Table 6. Initial Treatment Phase (Volume of Blood Taken) - Neonates

Procedure Subjects	Screening[a]	Day 1	Day 14	Day 42	Comments
Local Safety Labs[c] All Subjects	~1.0-4.0 mL[a]				Based on local site procedures
Central Safety Labs (Chemistry, Lipid, Hematology & Differential) All Subjects		2.3 mL		2.3 mL	
Serial PK and anti-FXa activity[b] Subjects taking apixaban			2.8 mL*	**	* 1.4 mL for each separate sample. **If one or both samples are not drawn during the Day 14 visit, then the procedure should be repeated at the Day 42 visit to obtain the missing sample(s).
Day 1 PK PK Cohort Neonates only[d]		1.5 mL[e]			
Total APIXIBAN (Potential) Maximum Blood Volume (mL)	**≤4 mL**[a]	**≤3.8 mL**	**2.8 mL**	**2.3 mL**	**Total: ≤12.9 mL PK Cohort**[c] (for post PK cohort: ≤11.4 mL)
Total SOC (Potential) Maximum Blood Volume (mL)	**≤4 mL**[a]	**2.3 mL**		**2.3 mL**	**Total: ≤8.6 mL**

a. To satisfy eligibility requirements, up to 4 mL of blood may be drawn within 7 days prior to randomization. These should be the most recent, local laboratory tests. Maximum blood volumes will be based on the child's weight and in accordance with local thresholds.

b. If possible, obtain within 24 hours of any major bleed or thrombotic event and record time of last dose prior to the event.

c. Lab tests include platelets, serum creatinine, ALT, conjugated bilirubin INR, pregnancy test. Pregnancy test will be collected in women of childbearing potential only.

d. Only for neonates recruited prior to completion of the neonate PK sub-analysis.

e. If DBS PK method is used, this will reduce the blood volume collected at this visit from 1.5 mL to 135 microliters (µL). Note: each DBS sample will require 45 µL (times 3 samples) over 24 hours.

7.3. Laboratory Assessments

The following laboratory tests are required to satisfy the exclusion criteria for this study and should be analyzed by the local laboratory and reviewed prior to randomization: platelets, serum creatinine, eGFR, ALT, conjugated bilirubin, and pregnancy test when applicable. Only the most recent laboratory results, obtained within 7 days prior to randomization, may be used to satisfy this requirement.

Blood samples for analysis by a central laboratory will be obtained during the Day 1 and Day 42 visits (and when applicable, Days 126 and 168) to establish baseline values and to assess safety. Note for subjects <2 years of age, local labs may be done in place of central laboratory tests and noted in the appropriate CRF to provide the required laboratory parameters for evaluation.

For central laboratory assessments, materials and detailed instructions for specimen collection, processing, storage and shipment will be provided in special kits and will be described in a separate laboratory manual.

7.3.1. Platelet Assessment and Treatment Guidelines for Thrombocytopenia

Platelet counts should be $\geq 50 \times 10^9$ per liter (L) prior to randomization. There are no evidence-based guidelines for anticoagulation therapy in relation to platelet counts. Close monitoring of platelet count and careful watching for signs of bleeding may be necessary in children with an anticipated drop in platelet count due to comorbid conditions and treatments.

Apixaban

In the absence of any other coagulopathy, the following guidelines are recommended during the course of the study period with apixaban:

- Full-dose apixaban therapy for subjects with platelet count $\geq 50 \times 10^9$ per L;
- Hold apixaban for platelet count $< 50 \times 10^9$ per L and restart when platelet count $\geq 50 \times 10^9$ per L or presumed to be above this threshold following a platelet transfusion.

Standard of Care

SOC should be managed according to local practice.

7.3.2. Estimated Glomerular Filtration Rate Assessment

The enrollment criterion for eGFR will be estimated based on the Schwartz formula [Schwartz et al, 2009].[27]

Inadequate renal function is defined as <30% of 1 standard deviation (SD) below normal GFR for age and size as determined by the Schwartz formula [eGFR ($ml/min/1.73m^2$) = 0.413 * (height (cms)/serum creatinine (mg/dL) for ages up to 2 years. Beyond 2 years of age, the qualifying GFR for this study is ≥ 30 $mL/min/1.73m^2$. 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].

Age (Gender)	Normal GFR (Mean GFR±SD) (mL/min/1.73m^2)	Qualifying GFR for enrollment* (Mean GFR) (mL/min/1.73m^2)
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

*Subject may be enrolled if GFR is at or greater than this value as determined by Schwartz formula.

7.3.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, on Days 1, 14, 42, and at the end of treatment visit. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at visits on Day 14, Day 42 and at the end of the study to confirm the subject has not become pregnant during the study. A negative pregnancy result is required. In the case of a positive confirmed pregnancy, the subject on apixaban will be withdrawn from study medication and the subject on SOC will be managed per local practice, but in either case the subject may remain in the study. Pregnancy tests may also be repeated as per request of the institutional review board (IRB)/ethics committees (EC) or if required by local regulations.

7.4. Pharmacokinetic and Pharmacodynamic Assessment

7.4.1. Sampling Time Points

Subjects on apixaban in Groups 1-4 will have PK/PD samples drawn during the Day 14 visit. On the day of the Day 14 visit, the subject will refrain from taking the apixaban dose until the pre-dose sample is drawn. After the sample is drawn, the subject will be administered the apixaban dose. A second PK/PD sample will be drawn between 2 and 4 hours after administration of the apixaban dose. All efforts will be made to obtain the PK/PD samples at the exact nominal time relative to dosing. In addition, the date and time of administration for the last 6 doses of apixaban prior to a pre-dose PK/PD sample on the day of the Day 14 visit will be recorded. Anti-FXa activity will be measured as a PD assessment using an aliquot from the plasma of the PK/PD sample. If DBS is the method of choice, a hematocrit result must have been drawn and available from a local laboratory within 48-72 hours prior to each PK sample timepoint (Day 1 for PK cohort, Day 14 and/or Day 42 for PK and post PK cohort).

If one or both samples are not drawn during the Day 14 visit, then the procedure should be repeated at the Day 42 visit to obtain the missing sample(s). If viable samples are not obtained on Day 14 or Day 42, the site monitor should be notified.

If possible, blood samples for apixaban concentration and anti-FXa activity should be obtained within 24 hours of any major bleed or thrombotic event along with the time of the last dose prior to the event.

Only for the apixaban treated neonates recruited into the study, prior to the completion of the neonate PK sub-analysis, PK samples will be drawn at 2-4, 12 ±1 and 24 ±1 hours after administration of the first apixaban dose of 0.1 mg on Day 1. The sample at 12- hour time-point should be collected prior to the second dose of apixaban on Day 1. The sample at 24- hour time-point should be collected prior to the first dose of apixaban on Day 2.

7.4.2. Plasma for Analysis of Apixaban Pharmacokinetic/Pharmacodynamic Samples

Samples will be analyzed for apixaban PK and anti-FXa activity using a validated analytical method in compliance with Pfizer standard operating procedures.

Materials and detailed instructions for specimen collection, processing, storage, shipment and contact information will be provided to the site.

7.5. Concomitant Medications

Prior medications will be recorded at Screening and Day 1 (baseline) (any medications during the last 30 days) prior to randomization. Concomitant medications will be recorded at each study visit following the first dose of investigational product up to the end of treatment (EOT) visit as indicated in the Schedule of Activities.

7.6. Adjudication of Safety and Efficacy Endpoints

All components of primary efficacy and safety endpoint will be adjudicated by blinded, independent adjudication committee.

There are four types of adjudication to be performed in this study as defined by the independent adjudication committee:

- Potential Symptomatic Efficacy Events (Packaged as Adverse Event (AE)/Serious Adverse Event (SAE)): All recurrent Venous Thromboembolic Events (VTE), All Stroke Events.
- Bleeding Events and Death Events: Major Bleeding, Clinically Relevant Non-Major Bleeding, Minor Bleeding, VTE Related Death, and All Cause Death.
- Interval Studies (IS): Recurrent VTE defined as either contiguous progression or non-contiguous new thrombus.

Further details on the adjudication process will be detailed in the Pfizer Adjudication Charter.

7.7. Bleeding Assessments

All bleeding events will be adjudicated by a blinded, independent adjudication committee as major bleeding, clinically relevant non-major bleeding, or minor bleeding. These endpoints are consistent with those recommended by the International Society on Thrombosis and Haemostasis for pediatric clinical trials in venous thromboembolism [Mitchell LG, 2011].[21] The adjudication committee will maintain the actual definitions used for adjudication. Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria, and are described as follows:

Major bleeding is defined as bleeding that satisfies one or more of the following criteria: a (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-h 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 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 subject'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 clinically relevant, non-major bleeding.

Although menstrual bleeding may result in a medical consultation and/or intervention, this will be classified as a minor bleeding event rather than clinically relevant non-major bleeding event.

All bruising events are reportable as a bleeding event.

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

7.7.1. Treatment Guidelines for Bleeding/Suspected Bleeding

Subjects with bleeding or suspected bleeding should undergo confirmatory laboratory or other testing [eg, ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI)], as indicated clinically. The date and time of the onset of the bleeding event will be recorded on the CRF.

The specific treatment for bleeding with SOC or apixaban is left to the discretion of the investigator and/or the attending physician based on the medical status of the subject and/or institutional policies. Table 7 provides information for the treatment of bleeding or suspected bleeding in subjects treated with apixaban.

Table 7. Treatment Guidelines for Bleeding/Suspected Bleeding in Subjects Treated with Apixaban

Minor Bleeding	Apixaban may or may not be held based on an individualized benefit-risk assessment
Clinically relevant non-major bleeding	Apixaban should be held. The following treatment measures may be considered: • Identify the source and institute local measures to stop the bleeding; • Perform laboratory test monitoring (eg, hemoglobin, INR, aPTT, platelet count, anti-Factor Xa activity); • Monitor apixaban using an anti-Factor Xa assay rather than the more standard coagulation tests (eg, INR, aPTT) which are less sensitive to apixaban; • If bleeding occurs up to 6 hours after apixaban dosing, administer activated charcoal oral solution to reduce apixaban plasma exposure; • Institute appropriate symptomatic treatment (eg, mechanical compression, surgical intervention, fluid replacement and hemodynamic support, blood product or component transfusion); • For bleeding that does not respond to local measures, administer fresh frozen plasma (FFP) as a supportive measure, recognizing that FFP does not reverse the anticoagulant effects of apixaban.
Major Bleeding	Apixaban should be held. The following treatment measures may be considered. • Administer recombinant Factor VIIa, however, there is no experience with this agent in apixaban-treated subjects. Its effectiveness for counteracting the effects of apixaban is not known. • Administer activated prothrombin complex concentrate (aPCC) or prothrombin complex concentrate (PCC, also referred to as factor IX concentrate), 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 up to 6 hours after apixaban dosing, administer activated charcoal oral solution to reduce apixaban plasma exposure.

Alternate treatments such as recombinant Factor VIIa have not been well evaluated in the pediatric population. There are few randomized clinical trials of recombinant Factor VIIa (rFVIIa, NovoSeven®) and approved anticoagulant therapies [Bijsterveld et al, 2002; Bijsterveld et al, 2004; Smith, 2002; Lankiewicz et al, 2006; Levi et al, 2010; Kessler, 2006; Leissinger et al, 2008].[5,6,28,15,17,13,16] There is no experience with rFVIIa and apixaban in adults or pediatrics. Some experts have recommended the use of prothrombin complex concentrate (PCC, also referred to as Factor IX concentrate) for reversal of anticoagulants such as warfarin. There are few randomized clinical trials in this area, but observational

studies and some guidelines are cited in support of this approach. There are a variety of PCC formulations available, which differ in their concentration of clotting factors (II, VII, IX and X). Dosing depends on body weight, the formulation of PCC employed, the degree of anticoagulation (INR), the clinical picture and whether concomitant FFP is also administered.

Thrombotic events have been reported with PCC use. Given the complexity of the dosing and the risks involved, it is recommended that the decision to employ a PCC for warfarin associated hemorrhage be made by an experienced clinician with careful evaluation of the risks and benefits. There are no data regarding the use of PCC for treatment of apixaban related hemorrhage.

The effect of activated charcoal on the pharmacokinetics of apixaban in healthy subjects was assessed in a Phase 1 clinical trial (CV185104). Administration of activated charcoal 2 and 6 hours after ingestion of a single oral dose of 20 mg apixaban reduced apixaban exposure (AUC) by approximately 50% and 27%, respectively. These data indicate that activated charcoal may be useful in managing exposure to apixaban several hours after apixaban administration.

7.8. Efficacy Assessments

The primary efficacy endpoint is the adjudicated composite of: (i) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism and (ii) VTE-related mortality. This endpoint is consistent with that recommended by the International Society on Thrombosis and Haemostasis for pediatric clinical trials in venous thromboembolism [Mitchell LG, 2011].[21] All components of the primary efficacy endpoint will be adjudicated by a blinded, independent adjudication committee.

Subjects will be assessed for signs or symptoms of VTE (eg, swelling, localized pain, redness, heat, localized warmth, unexplained shortness of breath, chest pain that gets worse with a deep breath, coughing or chest movement or coughing up blood) throughout the course of the study (inclusive of treatment and follow-up periods). If signs and symptoms are present, then subjects will undergo a diagnostic examination to confirm recurrence of VTE. Suspected VTE that occurs at any time after enrollment should also be reported as an AE or a SAE. All VTE will be adjudicated by an independent central adjudication committee in a blinded manner.

Materials and detailed instructions for completing and submitting the required documentation to the adjudication committee will be provided to the sites. Investigators are encouraged to send the dossier to the adjudication committee for assessment within 2 weeks of awareness of the suspected outcome occurrence.

7.8.1. Imaging Assessments

- Children 2 years to <18 years: In addition to the radiologic images obtained to confirm the index event, new radiologic images of the index clot site will be obtained during the midpoint of the study (Day 42 ± 14 days), and at the end of treatment visit (Day 84 ± 7 days). If applicable, radiologic images may be obtained at Days 126 (EOT) or Day 168 (EOT) (refer to the Extension Phase SOA). At the midpoint and end of treatment visits, the investigator will reassess the index event and all areas around the index event that were scanned initially based on the clinical assessment, to account for the presence of any new asymptomatic clots. At the midpoint (Day 42) and end of treatment (Day 84) visits, radiologic images that require sedation or radiation are not required and may be omitted, if not medically necessary. In addition, when medically appropriate, new radiologic images will be obtained if recurrent VTE is suspected. All assessments obtained in the evaluation of symptomatic or asymptomatic recurrent VTEs will be adjudicated.

- Children < 2 years of age: For neonates (birth to ≤27 days) and children 28 days to <2 years of age, if the treatment duration is <12 weeks, a midpoint image may be omitted at the discretion of the Investigator.

- Additional imaging assessments can be performed at the discretion of the Investigator at any time during the study.

The study does not prohibit further monitoring via radiologic images as part of standard practice for the care of the patient.

7.8.2. Criteria for Thrombus Review by Adjudication Committee

The following criteria will be used during the adjudication of all submitted new or recurrent VTE:

- "Resolution": Complete disappearance of the thrombus compared to the index event.

- "Regression": Unequivocal decrease (>50%) of the total volume/mass of the thrombus compared to the index event.

- "Unchanged": No significant change in the extent (defined as <=50% change in volume/mass) or location of the thrombus compared to the index event.

- "Recurrence-Contiguous": Unequivocal increase (>50%) of the total volume/mass of the thrombus compared to the index event.

- "Recurrence-New":

    - Thrombus resolution followed by new thrombus formation in the same location as the index event; or

- New non-contiguous thrombus formation in a different location as the index event.

- "Indeterminate/Non-Diagnostic Study":

  - Thrombus present but due to poor image quality or incomplete imaging cannot determine if the thrombus is present due to poor image quality or incomplete imaging.

The full adjudication process and criteria for thrombus review is details in the Pfizer Adjudication Charter.

7.9. Palatability Assessment

For subjects receiving apixaban, palatability will be assessed at the Day 14 study visit. The assessment will be administered to the subject and/or legal guardian in the form of a questionnaire.

8. 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 (investigational product) 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.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, LIFE-THREATENING or DEATH to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.
5	DEATH	Results in death.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (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.

Adverse events 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).

8.1. Serious Adverse Events

A S**erious 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;
- 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 [eg, 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 8.7 for the definition of potential DILI).

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 8.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 8.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in this study:

- A visit to the emergency room or other hospital department <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 (eg, 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason);
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

8.1.1. Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events 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 must be collected that occur during the screening period and up to the follow-up visit (35 ±5 days after the EOT visit).

The investigator must also 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, SAE updates with follow-up information and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs and all SAE updates with follow-up information must be recorded on the SAE Report Form and submitted to BMS (or designee); pregnancies must be reported on a Pregnancy Surveillance Form (electronic or paper forms) and submitted to BMS (or designee).
>
> SAEs must also be reported as Adverse Events in the electronic Case Report Form (eCRF) and the event marked as 'serious'. Recording an Adverse Event and marking it 'serious' in the eCRF is not a substitute for reporting the SAE as described above.

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

In all cases, an SAE Reporting Form must be submitted as directed above. 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.

8.2. Nonserious Adverse Events

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

8.2.1. Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 8.1.1). 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.

8.3. Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) and the AE CRF page as appropriate:

- 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 (eg, anemia versus low hemoglobin value).

8.4. 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 (3 days) plus 30 days for a total of 33 days, the investigator must immediately notify the Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 8.1.1.

The study drug will be permanently discontinued in an appropriate manner.

Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 8.1.1.

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. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.5. Medication Error

A medication error is any:

- Unintentional error in the prescribing.
- Dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient or consumer.

The following are medication errors for Apixaban ONLY:

- Missed doses due to misunderstanding of the dosing schedule (ie, QD instead of BID).
- Four or more consecutive missed doses.
- A consistent dosing schedule outside of BID (ie, QD, TID, QID), unless otherwise directed.
- A consistent dose above or below that which was prescribed based on IRT.
- Extending the Week 1 dosing beyond Week 1.

8.6. Overdose

All occurrences of overdose must be reported as SAEs (see Section 8.1.1 for reporting details).

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 must be reported as an SAE (see Section 8.1.1 for reporting details).

8.7. Potential Drug Induced Liver Injury (DILI)

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

If at any time during the treatment period a subject's LFT results show:

An isolated elevation of either serum glutamic-pyruvic transaminase (SGPT) (ALT) or aspartate aminotransferase (AST) ≥5 x ULN AND/OR a direct (conjugated) bilirubin >2 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct (conjugated) bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT), creatine kinase (CK) as soon as possible (ie, within 3 days).

If the repeat tests indicate:

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

2. If the repeat ALT/AST ≥5 x ULN AND/OR the direct (conjugated) bilirubin is >2 x ULN, the study medication must be interrupted.

The study medication must be interrupted if:

- Clinical jaundice is present for 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

- 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 the 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 medical Monitor and Study Director and perform the following:

- PT, 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.

8.8. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, 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.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in an Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Efficacy and safety outcomes will be presented using descriptive statistics including but not limited to means and standard deviations for continuous variables along with counts and frequencies for discrete variables.

9.1. Sample Size Determination

This is a descriptive study, and there is no formal pre-defined hypothesis testing. Therefore, there is no power calculation for the sample size determination. Throughout the trial, the study team, in conjunction with regulators (ie, Food and Drug Administration [FDA]), will evaluate exposure duration, imaging results, and other aspects of the trial to determine if the data from the subjects in the trial are sufficient to address the objectives of the trial. It is expected that a sample size up to 250, increased from an original sample size of 150, is needed in order to provide a reasonable safety and pharmacokinetic database in pediatric subjects. A target of 30 subjects will be randomized into each of the following three age groups: (1) 12 to <18 years; (2) 2 to <12 years; (3) 28 days to <2 years. For age group 4, neonates (birth to ≤27 days), the sample size may be adjusted based on a PK sub-analysis that will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. The number of neonates on apixaban will not exceed 20 subjects.

9.2. Efficacy Analysis

Appropriate summary statistics as described at the beginning of this section will be presented for all efficacy endpoints. A summary of overall results along with summaries for each of the age group will be presented. The neonates who are enrolled under amendment 8 without 2 to 1 randomization will be excluded in the overall population efficacy endpoints analyses.

9.2.1. Analysis of Primary Endpoint

There is no planned hypothesis testing for primary endpoint. Primary endpoint will be summarized by treatment group. The event rates and their corresponding 95% confidence intervals will be presented for each treatment group.

9.2.2. Analysis of Secondary Endpoints

There is no planned hypothesis testing for secondary endpoint. Secondary endpoints will be summarized by treatment group. The event rates and their corresponding 95% confidence intervals will be presented for each treatment group.

9.3. Safety Analysis

There is no planned hypothesis testing for the primary safety endpoint. The primary safety endpoint 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 group.

9.4. Pharmacokinetic and Pharmacodynamic Analyses

The PK analysis population is defined as all subjects randomized to and treated with apixaban who have at least 1 concentration of apixaban. The PD analysis population is defined as all subjects randomized to and treated with apixaban who have at least 1 apixaban concentration and 1 corresponding anti-FXa activity measure.

A population PK (PPK) model will be developed for plasma concentration versus time data using nonlinear mixed effects modeling (NONMEM, Icon Development Solutions, USA). Model-derived population and individual PK parameters (eg, CL/F, Vc/F, KA) will be used to estimate C_{max}, C_{min}, and AUC in each subject. A PPK-PD model will be also developed for apixaban plasma concentration and measured anti-FXa activity versus time data. Model-derived population and individual parameters (eg, slope of anti-FXa activity vs apixaban concentration relationship) will be used to estimate maximum and minimum anti-FXa activity 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.

For Age Group 4, a PK sub-analysis will be performed using initial neonatal data to confirm an apixaban fixed dosing regimen for neonates as described in a separate analysis plan. This analysis will be performed to confirm a fixed dose regimen of apixaban in neonates, which achieves an exposure similar to the adult approved regimen of 10 mg twice daily for 7 days followed by 5 mg twice daily.

9.5. Interim Analysis

There is an interim analysis planned in this study. The interim analysis will be performed when all randomized subjects in age Groups 1, 2 and 3 have completed the required minimal treatment periods or have discontinued from the study. The objective of this interim analysis is to provide an interim clinical study report for age Groups 1, 2, and 3 while age Group 4 continues to enroll the targeted number of subjects.

9.6. Data Monitoring Committee

This study will use an EDMC. The EDMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the EDMC Charter. Apixaban PK data will be reviewed periodically by the Sponsor and will be provided to the EDMC at its request. The recommendations made by the EDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/ Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/ Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the study. This information should also be disclosed to participants during the informed consent process. All study participants should be informed about the outcome of the study.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited, he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements and recruitment materials approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of apixaban at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects/caregivers and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial United States Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the study is part of a multi-center study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. B0661037/CV185-325 Dose Selection Rationale for the Original Protocol (05 October 2015), Amendment 1 (20 July 2015), and Amendment 2 (31 August 2015) [APPENDIX 2 SUPERSEDES APPENDIX 1]

Population pharmacokinetic (PPK) models were developed for the adult VTE treatment population based on data from the Phase 2 and 3 VTE treatment clinical trials and for the pediatric population based on data from the pediatric PK/PD studies (CV185079 and CV185118). Dose selection in B0661037/CV185-325 is based on simulations using these models with the following key assumptions:

1. The pediatric PK/PD profile established in the pediatric PK/PD studies represents the PK/PD profile in the pediatric VTE treatment population.

2. Equivalent exposure from the doses proven to be safe and effective in adult VTE treatment studies will be similarly safe and effective in the targeted pediatric VTE treatment population.

A PPK analysis, incorporating data from Phase 1, 2 and 3 studies, was conducted to support the VTE treatment indication in adults.[1] Apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination. Table 8 provides a summary of the predicted daily steady-state apixaban exposure (AUCss) for adult VTE treatment patients with the 5 mg and 10 mg BID doses based on the PPK model.

Table 8. Predicted Apixaban Daily AUC at Steady-State in VTE Treatment Adult Population

Steady State Parameter (Units)	5 mg BID			10 mg BID		
	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)
Daily AUCss (ng*hr/mL)	2446 (2346, 2554)	1293 (1197, 1398)	4807 (4433, 5174)	4649 (4439, 4875)	2456 (2271, 2664)	9136 (8445, 9836)

Source: Table 24 in the PPK and E-R analyses report.[1]

CV185079 study was a multiple-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of apixaban in pediatric subjects from birth to <18 years with an indwelling central venous catheter. However, the study was terminated prior to completion due to poor enrolment attributed to the complexity of the study design. Apixaban concentrations were available from 6 subjects in Group 5A (age ≥12 to <18 years) and 2 subjects in Group 4A (age ≥6 to <12 years). CV185118 study is an ongoing single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. Apixaban concentrations are available for 15 subjects in Groups 3-5: 5 subjects from Group 5 (12 years to <18 years); 6 subjects from Group 4 (6 years to <12 years); 4 subjects from Group 3 (2 years to <6 years) as part of a pre-specified interim analysis.

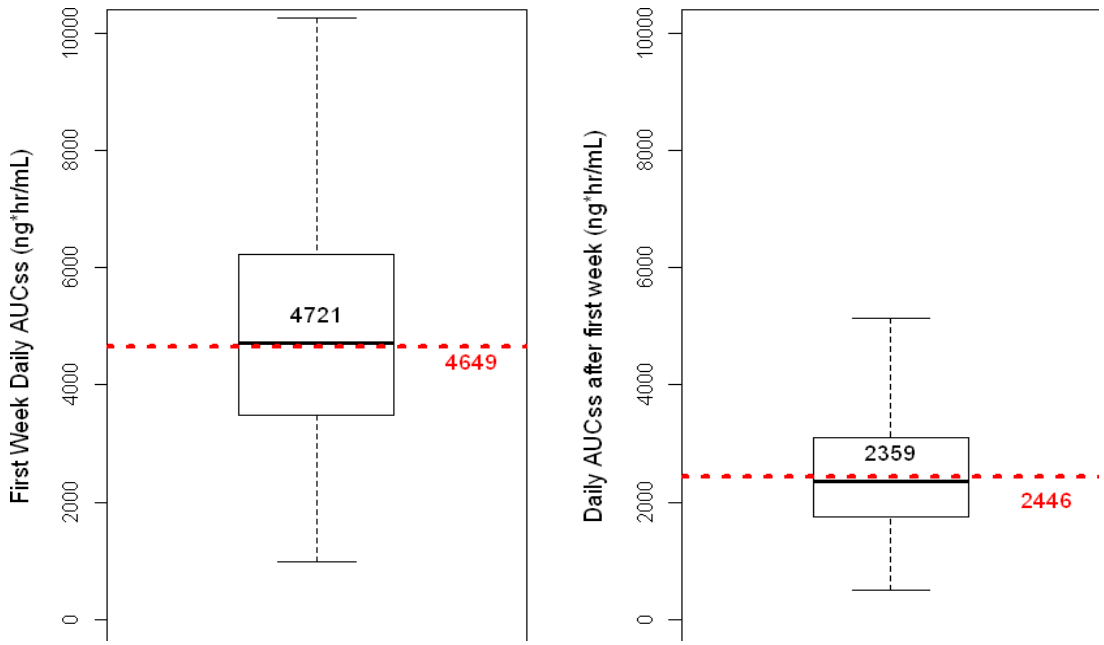
A pediatric PPK model was developed using the combined available data from Studies CV185118 and CV185079. This pediatric PPK analysis included a total of 144 apixaban concentrations from 23 subjects. A Bayesian analysis with an uninformative prior was used and apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination.

Using this interim pediatric PPK model, a PK simulation was performed to select doses for the oldest of 4 age groups in Study B0661037/CV185-325 (Age Group 1: 12 to <18 years) to achieve an exposure (daily AUCss) equivalent to that associated with a safe and effective dose regimen in the adult VTE treatment population (Table 8). A combined approach using fixed doses along with weight-based dosing was evaluated in the simulation, as shown below:

- Subjects between the ages of 12 to <18 years who are >40 kg will receive 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter.
- Subjects between the ages of 12 to <18 years who are ≤40 kg will receive a dose of 0.2 mg/kg twice daily for 7 days followed by 0.1 mg/kg twice daily thereafter.

A total of 2000 subjects were randomly sampled from the age range of 12 years to <18 years and the body weight was sampled from the Centers for Disease Control and Prevention growth chart based on each subject's age and sex. The PK simulation results are summarized as box-and-whisker plots in Figure 1. The results show that this dosing regimen is expected to achieve a median exposure that is similar to the median exposure in adults.

Figure 1. Box-and-Whisker Plot of Simulated Apixaban Daily AUC at Steady-State for Age Group 1 (12 to <18 years) During the First Week† (left) and After the First Week‡ (right)



Source: ePharmacology step ID: 543403
† 10 mg twice daily for 7 days followed by 5 mg twice daily for subjects in Age Group 1 who are >40 kg:
‡ 0.2 mg/kg twice daily for 7 days followed by 0.1 mg/kg twice daily for subjects in Age Group 1 who are ≤40 kg:
The horizontal black line and the black number within the box represent the median of the simulated data. The dotted red line and the red number represent the target exposure identified in the VTE treatment adult population. The height of the box is equal to the interquartile distance or IQD, which is the difference between the third and first quartiles of the data. The whiskers (the lines extending from the top and bottom of the box) extend to the nearest value not beyond a standard span from the quartiles, which is 1.5 times the IQD from the center of the data.

The ongoing CV185118 study will also enroll children in 2 younger age groups (from 2 years to <6 years and neonates to <2 years) in a phased approach. As PK data are obtained for these additional age groups, the PPK model will be updated and simulations will be performed to select doses for the 3 younger age groups of neonates, 28 days to <2 years, and 2 years to <12 year in Study B0661037/CV185-325.

In conclusion, the following doses are recommended in Age Group 1 based on the PK modeling and simulation:

- Subjects between the ages of 12 to <18 years who are >40 kg will receive 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter;

- Subjects between the ages of 12 to <18 years who are ≤40 kg will receive a dose of 0.2 mg/kg twice daily for 7 days followed by 0.1 mg/kg twice daily thereafter.

Reference

1. Population pharmacokinetic and exploratory exposure-response analyses of apixaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE. PMAR-00312, Pfizer Inc. 2013. BMS Document Control No. 930071141.

Appendix 2. B0661037/CV185-325 Dose Selection Rationale for Amendment 3 [APPENDIX 3 SUPERSEDES APPENDIX 2]

A population pharmacokinetic (PPK) model was developed for the adult VTE treatment population based on data from the Phase 2 and 3 VTE treatment clinical trials. For the pediatric population, a PPK model was developed using the data from the ongoing Study CV185118. Dose selection in B0661037/CV185-325 is based on simulations using these models with the following key assumptions:

1. The pediatric PK/PD profile established in the pediatric PK/PD studies represents the PK/PD profile in the pediatric VTE treatment population.

2. Equivalent exposure from the doses proven to be safe and effective in adult VTE treatment studies will be similarly safe and effective in the targeted pediatric VTE treatment population.

A PPK analysis, incorporating data from Phase 1, 2 and 3 studies, was conducted to support the VTE treatment indication in adults.[1] Apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination. Table 8 provides a summary of the predicted daily steady-state apixaban exposure (AUCss) for adult VTE treatment patients with the 5 mg and 10 mg BID doses based on the PPK model.

Table 8. Predicted Apixaban Daily AUC at Steady State in VTE Treatment Adult Population

Steady State Parameter (Units)	5 mg BID			10 mg BID		
	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)
Daily AUCss (ng*hr/mL)	2446 (2346, 2554)	1293 (1197, 1398)	4807 (4433, 5174)	4649 (4439, 4875)	2456 (2271, 2664)	9136 (8445, 9836)

Source: Table 24 in the PPK and E-R analyses report.[1]

CV185118 study is an ongoing single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As of 31-May-2019, a total of 46 subjects received apixaban in CV185118: 10 subjects 12 years to <18 years of age, 9 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, 9 subjects 28 days to <9 months, and 1 subject birth to <28 days.

The Interim Analysis 2 was completed using the available PK data from these subjects. A total of 147 apixaban concentrations were available from 28 subjects. A 2-compartment PPK model with first-order absorption and a dose dependent bioavailability adequately described the PK of apixaban in pediatric subjects. The estimated oral clearance of apixaban increased from 0.996 L/h in Group 2A (9 months to <2 years) to 4.77 L/h in Group 5 (12 years to <18 years). For pediatric subjects older than 12 years of age, oral clearance values are

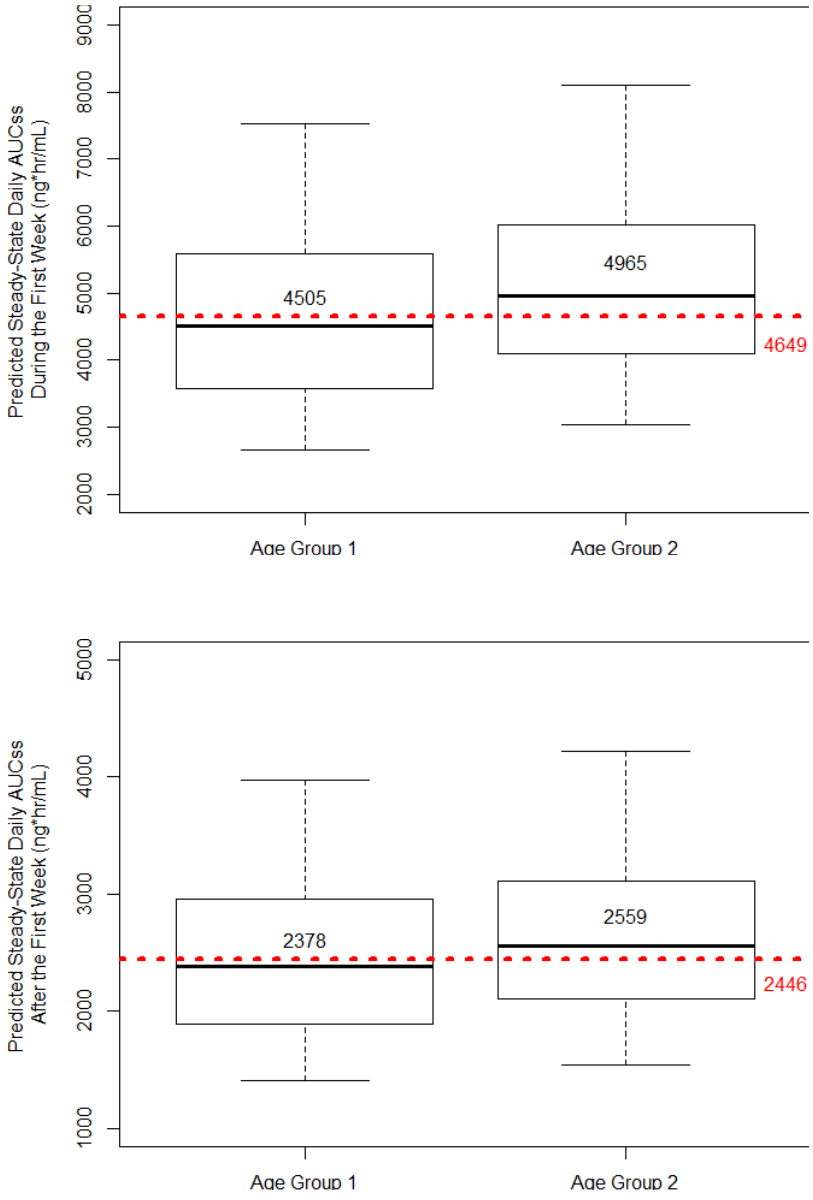
similar to those of adults. The body weight was an important covariate for oral clearance of apixaban. When modeled as a power function, the parameter estimate for the covariate effect of weight on oral clearance was 0.634 [95% CI: 0.506-0.762]. The magnitude of inter-individual variability in oral clearance is similar between adults and pediatric subjects (~30%).

Using this Interim Analysis 2 pediatric PPK model, a PK simulation was performed to select doses for the two oldest of 4 age groups in Study B0661037/CV185-325 (Age Group 1: 12 to <18 years and Age Group 2: 2 to <12 years) to achieve an exposure (daily AUC_{ss}) similar to that associated with a safe and effective dose regimen in the adult VTE treatment population (Table 8). Considering that apixaban oral clearance was dependent upon the body weight in pediatric subjects older than 2 years in CV185118, consistent with reported values for allometric scaling,[2] a uniform mg/kg approach for both Age Group 1 and Age Group 2 was evaluated for simplified and accurate dosing. In addition, the body weight cut-off was changed from 40 kg to 35 kg to ensure a smooth transition of doses between administration with oral solution and tablets. A combined approach using fixed doses along with weight-based dosing was evaluated in the simulation, as shown below:

- Subjects between the ages of 2 to <18 years who are ≥35 kg will receive 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter;
- Subjects between the ages of 2 to <18 years who are <35 kg will receive a dose of 0.28 mg/kg twice daily for 7 days followed by 0.14 mg/kg twice daily thereafter.

A total of 4000 subjects (2000 subjects for each Age Group) were randomly sampled from the age range of 2 years to <18 years and the body weight was sampled from the Centers for Disease Control and Prevention growth chart based on each subject's age and sex. The PK simulation results are summarized as box-and-whisker plots in Figure 2. The results show that this dosing regimen is expected to achieve a median exposure that is similar to the median exposure in adults.

Figure 2. Box-and-Whisker Plot of Simulated Apixaban Daily AUC at Steady-State for Age Group 1 (12 to <18 years) and Age Group 2 (2 to <12 years) During the First Week (top) and After the First Week (bottom) Using the Proposed Dosing†



Source: ePharmacology step ID: 651577
† 10 mg twice daily for 7 days followed by 5 mg twice daily for subjects who are ≥35 kg:
0.28 mg/kg twice daily for 7 days followed by 0.14 mg/kg twice daily for subjects who are <35 kg:

The horizontal black line and the black number within the box represent the median of the simulated data. The dotted red line and the red number represent the target exposure identified in the VTE treatment adult population. For box and whisker plots, Median = center line within box, 25th and 75th percentiles = lower and upper box boundaries, 90% Prediction intervals = whiskers.

The ongoing CV185118 study will also enroll children in younger age groups (neonates to <2 years) in a phased approach. As PK data are obtained for these additional age groups, the PPK model will be updated and simulations will be performed to select doses for the younger age groups of neonates and 28 days to <2 years in Study B0661037/CV185-325.

In conclusion, the following doses are recommended in Age Groups 1 and 2 based on the PK modeling and simulation:

- Subjects between the ages of 2 to <18 years who are ≥35 kg will receive 10 mg twice daily for 7 days followed by 5 mg twice daily thereafter;

- Subjects between the ages of 2 to <18 years who are <35 kg will receive a dose of 0.28 mg/kg twice daily for 7 days followed by 0.14 mg/kg twice daily thereafter.

Reference

1. Population pharmacokinetic and exploratory exposure-response analyses of apixaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE. PMAR-00312, Pfizer Inc. 2013. BMS Document Control No. 930071141.

2. Liu T, Ghafoori P, Gobburu JV., Allometry Is a Reasonable Choice in Pediatric Drug Development. J Clin Pharmacol. 2016 Sep 21 [Epub ahead of print].

Appendix 3. B0661037/CV185-325 Dose Selection Rationale for Amendment 4

A population pharmacokinetic (PPK) model was developed for the adult VTE treatment population based on data from the Phase 2 and 3 VTE treatment clinical trials. For the pediatric population, a PPK model was developed using the data from the ongoing Study CV185118. Dose selection in B0661037/CV185-325 is based on simulations using these models with the following key assumptions:

1. The pediatric PK/PD profile established in the pediatric PK/PD studies represents the PK/PD profile in the pediatric VTE treatment population.

2. Equivalent exposure from the doses proven to be safe and effective in adult VTE treatment studies will be similarly safe and effective in the targeted pediatric VTE treatment population.

A PPK analysis, incorporating data from Phase 1, 2 and 3 studies, was conducted to support the VTE treatment indication in adults.[1] Apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination. Table 8 provides a summary of the predicted daily steady-state apixaban exposure (AUCss) for adult VTE treatment patients with the 5 mg and 10 mg BID doses based on the PPK model.

Table 8. Predicted Apixaban Daily AUC at Steady State in VTE Treatment Adult Population

Steady State Parameter (Units)	5 mg BID			10 mg BID		
	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)
Daily AUCss (ng*hr/mL)	2446 (2346, 2554)	1293 (1197, 1398)	4807 (4433, 5174)	4649 (4439, 4875)	2456 (2271, 2664)	9136 (8445, 9836)

Source: Table 24 in the PPK and E-R analyses report.[1]

CV185118 study is an ongoing single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As of 09 Dec 2016, a total of 34 subjects received apixaban with complete enrollment of age groups of 28 days to <18 years of age: 8 subjects 12 years to <18 years of age, 8 subjects 6 years to <12 years of age, 8 subjects 2 years to <6 years of age, 6 subjects 9 months to <2 years of age, and 4 subjects 28 days to <9 months.

The Interim Analysis 3 was completed using the available PK data from these subjects. A total of 180 apixaban concentrations were available from 34 subjects. A 2-compartment PPK model with first-order absorption and a dose dependent bioavailability adequately described the PK of apixaban in pediatric subjects. The apparent oral clearance of apixaban in pediatric subjects was characterized using allometric scaling with the estimated power function of 0.624 [95% CI: 0.538-0.710][2] and a fixed maturation function based on the apixaban elimination profile and known ontogeny of those pathways.[3]

The estimated oral clearance of apixaban increased from 0.996 L/h in Group 2A (9 months to <2 years) to 4.77 L/h in Group 5 (12 years to <18 years). For pediatric subjects older than 12 years of age, oral clearance values are similar to those of adults. Body weight was an important covariate for oral clearance of apixaban. In addition, oral clearance, when normalized to body weight, was constant across the pediatric age range of 3 months to 18 years. The magnitude of inter-individual variability in oral clearance is similar between adults and pediatric subjects (~30%).

With the introduction of 0.5 mg tablets in Amendment 4, the dosing paradigm of apixaban changed from mg/kg dosing (Appendix 1 and Appendix 2) to fixed-dose, body weight-tiered regimen, as outlined in Table 9. The fixed-dose, body weight-tiered regimen uses apixaban doses in increments of 0.5 mg according to the appropriate weight range, regardless of apixaban formulations (ie, oral solution or 0.5 mg tablets).

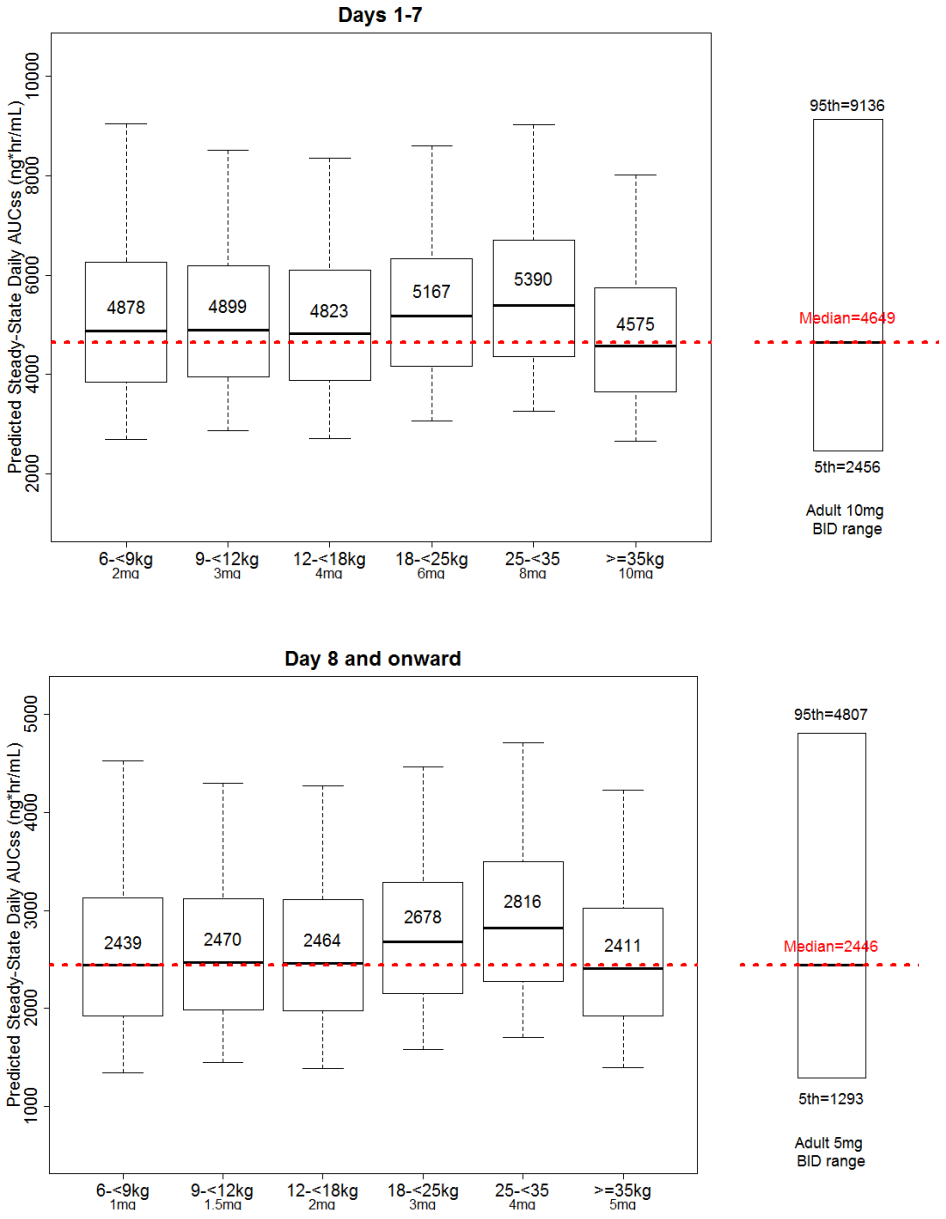
Table 9. Fixed Dose Body Weight Tiered Regimen in B0661037 for Pediatric Subjects >3 Months of Age and >6 kg of Body Weight

	6 to <9 kg[†]	9 to <12 kg[†]	12 to <18 kg[†]	18 to <25 kg[†]	25 to <35 kg[†]	≥35 kg
Days 1-7	2 mg BID	3 mg BID	4 mg BID	6 mg BID	8 mg BID	10 mg BID
Day 8 onward	1 mg BID	1.5 mg BID	2 mg BID	3 mg BID	4 mg BID	5 mg BID

[†] Subjects will receive fixed-dose using apixaban oral solution or 0.5 mg tablets
BID: twice daily

A total of 30000 simulated subjects (10000 subjects for each Age Group [Age Group 1: 12 <18 years for, Age Group 2: 2-<12 years, and Age Group 3: 28 days -<2 years]) were randomly sampled from the Centers for Disease Control and Prevention growth chart based on each subject's age and sex. Simulated subjects whose body weight was less than 6 kg or age was less than 3 months were removed. The final PK simulation results are summarized as box-and-whisker plots for each weight tier in Figure 3. The PK simulation had 2686, 4819, 4551, 3018, 2999, and 10917 simulated subjects for 6 to <9 kg, 9 to <12 kg, 12 to <18 kg, 18 to <25 kg, 25 to <35 kg, and ≥35 kg tiers, respectively. The results show that this fixed-dose body weight tiered regimen is expected to achieve a median exposure that is similar to the median exposure in adults.

Figure 3. Box-and-Whisker Plot of Simulated Apixaban Daily AUC at Steady-State for Body Weight-Tiers During the First Week (Top) and After the First Week (Bottom) Using the Proposed Dosing in subjects ≥3 Months of Age and ≥6 kg of Body Weight



Source: ePharmacology step ID: 684747
The horizontal black line and the black number within the box represent the median of the simulated data. The dotted red line and the red number represent the target exposure identified in the VTE treatment adult population. For box and whisker plots, Median = center line within box, 25th and 75th percentiles = lower and upper box boundaries, 90% Prediction intervals = whiskers.
The range of predicted apixaban daily AUC in VTE Treatment adults is represented as a box on the right of the plots: Median = horizontal black line within the box, 5th and 95th percentiles = lower and upper box boundaries.

The ongoing CV185118 study will also enroll children in the youngest age group of neonates. As PK data are obtained for these additional age groups, the PPK model will be updated and simulations will be performed to select doses for the younger age groups of neonates and 28 days to <3 months in Study B0661037/CV185-325.

In conclusion, the fixed doses in Table 9 are recommended in subjects ≥3 months of age and ≥6 kg of body weight based on the PK modeling and simulation.

Reference

1. Population pharmacokinetic and exploratory exposure-response analyses of apixaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE. PMAR-00312, Pfizer Inc. 2013. BMS Document Control No. 930071141.

2. Liu T, Ghafoori P, Gobburu JV., Allometry Is a Reasonable Choice in Pediatric Drug Development. J Clin Pharmacol. 2016 Sep 21 [Epub ahead of print].

3. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants, and children. Clinical Pharmacokinetics 2006; 45(9): 931-956.

Appendix 4. B0661037/CV185-325 Dose Selection Rationale for Amendment 6

A population pharmacokinetic (PPK) model was developed for the adult VTE treatment population based on data from the Phase 2 and 3 VTE treatment clinical trials. For the pediatric population, a PPK model was developed using the data from the ongoing Study CV185118. Dose selection in B0661037/CV185-325 is based on simulations using these models with the following key assumptions:

1. The pediatric PK/PD profile established in the pediatric PK/PD studies represents the PK/PD profile in the pediatric VTE treatment population.

2. Equivalent exposure from the doses proven to be safe and effective in adult VTE treatment studies will be similarly safe and effective in the targeted pediatric VTE treatment population.

A PPK analysis, incorporating data from Phase 1, 2 and 3 studies, was conducted to support the VTE treatment indication in adults.[1] Apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination. Table 8 provides a summary of the predicted daily steady-state apixaban exposure (AUCss) for adult VTE treatment patients with the 5 mg and 10 mg BID doses based on the PPK model.

Table 8. Predicted Apixaban Daily AUC at Steady-State in VTE Treatment Adult Population

Steady State Parameter (Units)	5 mg BID			10 mg BID		
	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)
Daily AUCss (ng*hr/mL)	2446 (2346, 2554)	1293 (1197, 1398)	4807 (4433, 5174)	4649 (4439, 4875)	2456 (2271, 2664)	9136 (8445, 9836)

Source: Table 24 in the PPK and E-R analyses report.[1]

CV185118 study is an ongoing single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As of May 31, 2019, a total of 46 subjects received apixaban in CV185118: 10 subjects 12 years to <18 years of age, 9 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, 9 subjects 28 days to <9 months, and 1 subject birth to <28 days. CV185079 study was a multiple-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of apixaban in pediatric subjects, which was terminated due to poor enrolment. Apixaban concentrations were available from 6 subjects with age 12 to <18 years and 2 subjects with age 6 to <12 years in CV185079.

The Interim Analysis 3C was completed using the available PK data from these subjects in CV185118 and CV185079. Consistent with the previous IA3, the pediatric data were enriched with data from additional clinical studies in healthy young adults to support the pediatric population PK analysis. A total of 287 apixaban concentrations were available from 54 subjects. A 2-compartment PPK model with first-order absorption and a dose dependent bioavailability adequately described the PK of apixaban in pediatric subjects. The apparent oral clearance of apixaban in pediatric subjects was characterized using allometric scaling with the estimated power function of 0.704 [95% CI: 0.651 - 0.756][2] and a fixed maturation function based on the apixaban elimination profile and known ontogeny of those pathways.[3]

The estimated oral clearance of apixaban increased with increasing age. For pediatric subjects older than 12 years of age, oral clearance values are similar to those of adults. Body weight was an important covariate for oral clearance of apixaban. In addition, oral clearance, when normalized to body weight, was generally constant across the pediatric age range of 28 days to 18 years, except for the neonate subject. The magnitude of inter-individual variability in oral clearance is similar between adults and pediatric subjects (~30%).

The fixed-dose body weight-tiered regimen is shown in Table 10.

Table 10. Fixed-Dose Body Weight-Tiered Regimen in B0661037 for Pediatric Subjects in ≥28 Days of Age and ≥4 Kg of Body Weight

	4 to <5 kg†	5 to <6 kg†	6 to <9 kg†	9 to <12 kg†	12 to <18 kg†	18 to <25 kg†	25 to <35 kg†	≥35 kg
	Doses proposed in Amendment 6		Doses selection in current protocol					
Days 1-7	0.6 mg BID	1 mg BID	2 mg BID	3 mg BID	4 mg BID	6 mg BID	8 mg BID	10 mg BID
Day 8 onward	0.3 mg BID	0.5 mg BID	1 mg BID	1.5 mg BID	2 mg BID	3 mg BID	4 mg BID	5 mg BID

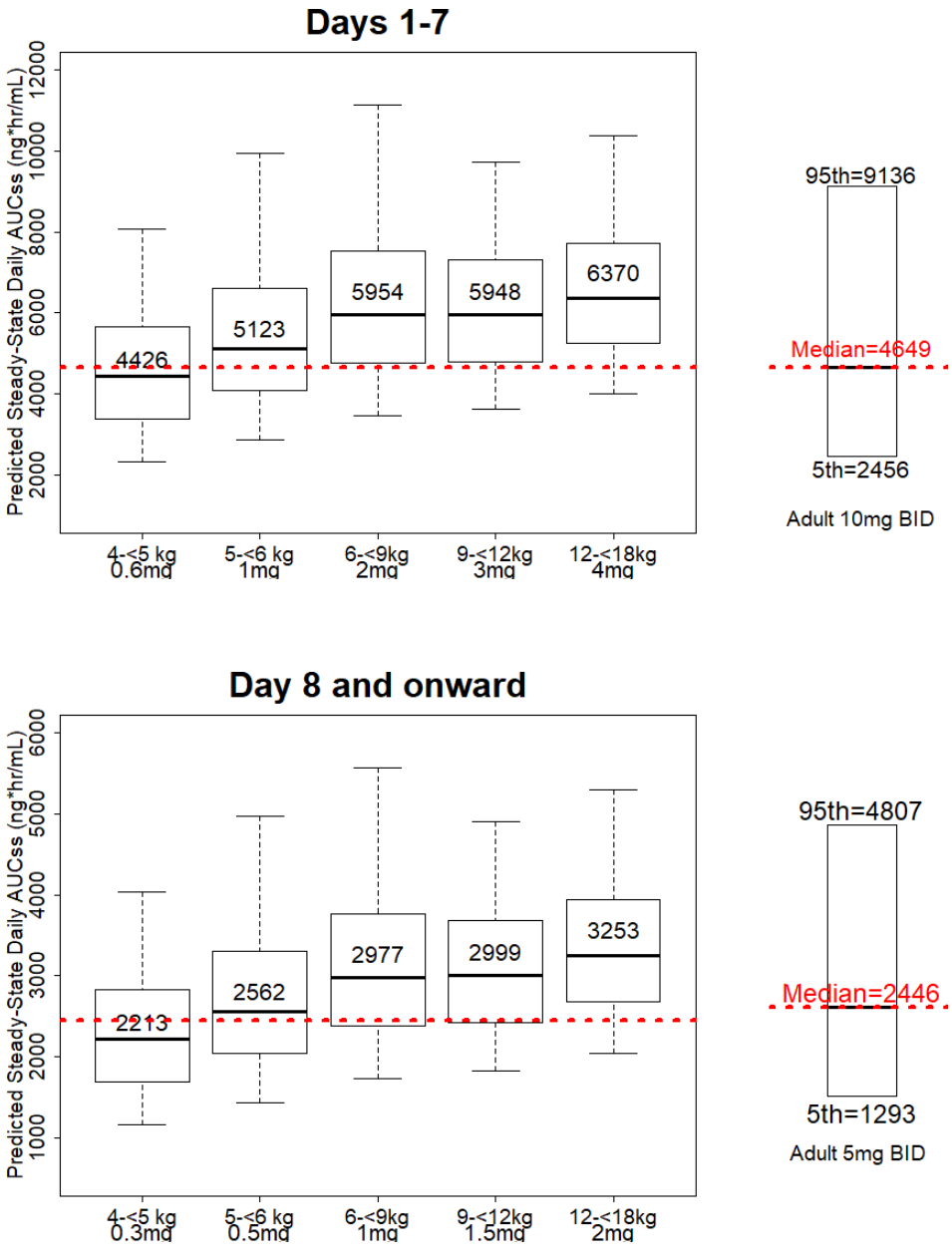
† Subjects will receive fixed-dose using apixaban oral solution or 0.5 mg tablets.
BID: twice daily

A total of 30000 simulated subjects (10000 subjects for each Age Group [Age Group 1: 12 <18 years for, Age Group 2: 2-<12 years, and Age Group 3: 28 days -<2 years]) were randomly sampled from the Centers for Disease Control and Prevention growth chart based on each subject's age and sex. Simulated subjects whose body weight was less than 4 kg or age was less than 28 days were removed. Since the enrollment of subjects 2 to <18 years is closed as of May 10, 2019, simulation subjects ≥2 years were also removed.

The final PK simulation results are summarized as box-and-whisker plots for each weight tier in Figure 4. The PK simulation had 286, 567, 2771, 4548, and 1559 simulated subjects for 4 to <5 kg, 5 to <6 kg, 6 to <9 kg, 9 to <12 kg, and 12 to <18 kg tiers, respectively. No subjects <2 year were simulated to have body weight ≥18 kg based on the growth chart. The results show that this fixed-dose body weight tiered regimen in the newly proposed 4-<6 kg tiers is expected to achieve a median exposure that is similar to the median exposure in adults. While the simulation using the IA3C final model predicted ~30% increase in

exposure in subjects ≥6 kg, this is not considered clinically significant as a similar magnitude of difference has been observed in various subgroups of adults without affecting benefit risk of apixaban (ie, females versus males, low versus high body weight groups).

Figure 4. Box-and-Whisker Plot of Simulated Apixaban Daily AUC at Steady-State for Body Weight-Tiers During the First Week (Top) and After the First Week (Bottom) Using the Proposed Dosing in subjects ≥28 Days to <2 Years of Age



Source: ePharmacology step ID: AS759401.

The horizontal black line and the black number within the box represent the median of the simulated data. The dotted red line and the red number represent the target exposure identified in the VTE treatment adult population. For box and whisker plots, Median = center line within box, 25th and 75th percentiles = lower and upper box boundaries, 90% Prediction intervals = whiskers.

The range of predicted apixaban daily AUC in VTE Treatment adults is represented as a box on the right of the plots: Median = horizontal black line within the box, 5th and 95th percentiles = lower and upper box boundaries.

The ongoing CV185118 study will also enroll children in the youngest age group of neonates. As PK data are obtained for these additional age groups, the PPK model will be updated and simulations will be performed to select doses for the younger age groups of neonates and 28 days to <3 months in Study B0661037/CV185-325.

In conclusion, the proposed doses in Table 10 are recommended in subjects ≥28 days to <2 years of age and ≥4 kg of body weight based on the PK modeling and simulation.

Reference

1. Population pharmacokinetic and exploratory exposure-response analyses of apixaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE. PMAR-00312, Pfizer Inc. 2013. BMS Document Control No. 930071141.

2. Liu T, Ghafoori P, Gobburu JV., Allometry Is a Reasonable Choice in Pediatric Drug Development. J Clin Pharmacol. 2016 Sep 21 [Epub ahead of print].

3. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants, and children. Clinical Pharmacokinetics 2006; 45(9): 931-956.

Appendix 5. B0661037/CV185-325 Dose Selection Rationale for Age Group 4 (≤27 Days of Age) in Amendment 7- PK Cohort Neonates

A population pharmacokinetic (PPK) model was developed for the adult VTE treatment population based on data from the Phase 2 and 3 VTE treatment clinical trials. For the pediatric population, a PPK model was developed using the data from the ongoing Study CV185118. Dose selection in B0661037/CV185-325 is based on simulations using these models with the following key assumptions:

1. The pediatric PK/PD profile established in the pediatric PK/PD studies represents the PK/PD profile in the pediatric VTE treatment population.

2. Equivalent exposure from the doses proven to be safe and effective in adult VTE treatment studies will be similarly safe and effective in the targeted pediatric VTE treatment population.

A PPK analysis, incorporating data from Phase 1, 2 and 3 studies, was conducted to support the VTE treatment indication in adults.[1] Apixaban exposure was adequately characterized by a 2-compartment PPK model with first-order absorption and first-order elimination.[2] provides a summary of the predicted daily steady-state apixaban exposure (AUCss) for adult VTE treatment patients with the 5 mg and 10 mg BID doses based on the PPK model.

Table 11. Predicted Apixaban Daily AUC at Steady State in VTE Treatment Adult Population

Steady State Parameter (Units)	5 mg BID			10 mg BID		
	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)	Median (90% CI)	5th Percentile (90% CI)	95th Percentile (90% CI)
Daily AUCss (ng*hr/mL)	2446 (2346, 2554)	1293 (1197, 1398)	4807 (4433, 5174)	4649 (4439, 4875)	2456 (2271, 2664)	9136 (8445, 9836)

Source: Table 24 in the PPK and E-R analyses report.[1]

CV185118 study is an ongoing single-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in pediatric subjects from birth to <18 years at risk for a venous or arterial thrombotic disorder. As of May 31, 2019, a total of 46 subjects received apixaban in CV185118: 10 subjects 12 years to <18 years of age, 9 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, 9 subjects 28 days to <9 months, and 1 subject birth to <28 days. CV185079 study was a multiple-dose study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of apixaban in pediatric subjects, which was terminated due to poor enrolment. Apixaban concentrations were available from 6 subjects with age 12 to <18 years and 2 subjects with age 6 to <12 years in CV185079.

The Interim Analysis 3C was completed using the available PK data from these subjects in CV185118 and CV185079. Consistent with the previous IA3, the pediatric data were enriched with data from additional clinical studies in healthy young adults to support the pediatric population PK analysis. A total of 287 apixaban concentrations were available from 54 subjects. A 2-compartment PPK model with first-order absorption and a dose dependent bioavailability adequately described the PK of apixaban in pediatric subjects. The apparent oral clearance of apixaban in pediatric subjects was characterized using allometric scaling with the estimated power function of 0.704 [95% CI: 0.651 - 0.756][2] and a fixed maturation function based on the apixaban elimination profile and known ontogeny of those pathways.[3]

The estimated oral clearance of apixaban increased with increasing age. For pediatric subjects older than 12 years of age, oral clearance values are similar to those of adults. Body weight was an important covariate for oral clearance of apixaban. In addition, oral clearance, when normalized to body weight, was generally constant across the pediatric age range of 28 days to 18 years. The magnitude of inter-individual variability in oral clearance is similar between adults and pediatric subjects (~30%).

For the first 5 neonates (≤27 days of age) randomized to apixaban, subjects will receive standard of care therapies for at least 5 days and then will receive apixaban 0.1 mg twice daily. To support this dose selection, a total of 10000 simulated neonate subjects was randomly sampled from the Centers for Disease Control and Prevention growth chart based on each subject's age and sex. Simulated subjects had a body weight of 2.6 kg to less than 6 kg and an age of 6 days to less than 28 days considering at least 5 days of SOC treatment prior to apixaban administration.

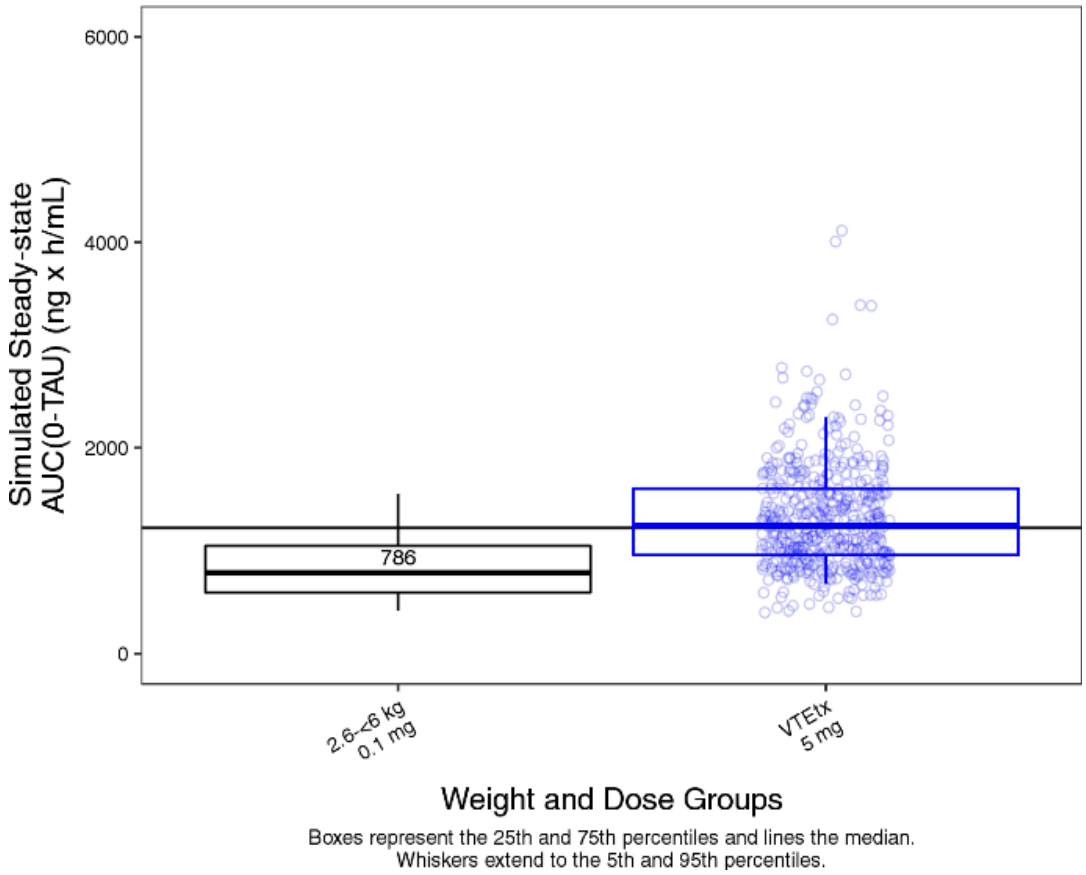
The PK simulation results are summarized as box-and-whisker plot in Figure 5.

The results show that the initial dose of 0.1 mg twice daily for neonates is expected to result in a slightly lower exposure (~30%) than that in adults with 5 mg twice daily but are generally consistent with the range in adults. Thus, this dose is considered safe and effective for neonates who will have been treated with standard of care therapies for ≥5 days.

For each neonate, a series of blood samples will be collected after the first 0.1 mg dose of apixaban to predict each subject's daily apixaban exposure (AUCss) at steady-state. If the subject's predicted AUCss is outside the 90% prediction interval from adults with 5 mg twice daily (1293 ng*hr/mL to 4807 ng*hr/mL in Table 11), apixaban dose will be adjusted to remain within this interval.

Once 5 neonates are enrolled, a pharmacokinetic analysis will be conducted using apixaban exposure data to confirm a fixed dose regimen of apixaban in neonates to achieve an exposure similar to the approved apixaban regimen in adults (10 mg BID for 7 days followed by 5 mg BID).

Figure 5. Box-and-Whisker Plot of Simulated Apixaban AUC(0-TAU) at Steady-State for Neonates with 0.1 mg Twice Daily in Group 4



The horizontal black line and the black number within the box represent the median of the simulated data. The solid blue line represents the target exposure identified in the VTE treatment adult population. The blue boxplot to the far right with blue dots overlaid represents model-estimated AUC(0-$_{TAU}$) in VTE adults with 5 mg BID. For box and whisker plots, Median = center line within box, 25th and 75th percentiles = lower and upper box boundaries, 90% prediction intervals = whiskers.

Abbreviation: AUC(0-$_{TAU}$)=area under the concentration-time curve from time 0 to the end of the dosing interval.

[redacted]

Reference

1. Population pharmacokinetic and exploratory exposure-response analyses of apixaban for the treatment of DVT and PE and for the prevention of recurrent DVT and PE. PMAR-00312, Pfizer Inc. 2013. BMS Document Control No. 930071141.

2. Liu T, Ghafoori P, Gobburu JV., Allometry Is a Reasonable Choice in Pediatric Drug Development. J Clin Pharmacol. 2016 Sep 21 [Epub ahead of print].

3. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants, and children. Clinical Pharmacokinetics 2006; 45(9): 931-956.

Appendix 6. B0661037/CV185-325 Summary of Changes

Document	Version Date	Summary of Changes and Rationale
Amendment 7	12 February 2020	1. Protocol Summary updated to reflect the summary of changes made throughout the protocol amendment. 2. Protocol Summary, Study Treatment: Text and Table 1 updated to include information on the dosing of neonates. 3. Table 1 footnote c, Table 2 footnote c, Section 4.1 Inclusion Criteria, and Section 5.1 Allocation to Treatment updated with new definition of a neonate. 4. Schedule of Activities (SOA), footnote a updated to state that a subject randomized as a neonate, should have his/her weight checked at 28 days of life, at an unplanned visit, to see if a dose adjustment needs to be made. In addition, a clarifying statement added regarding potential dose adjustments for all patients <2 years old. 5. SOA updated to include Day 1 apixaban pharmacokinetic (PK) sampling for neonates recruited prior to the completion of the neonate PK sub-analysis. Corresponding footnote "f" added for clarification. 6. Protocol Summary and SOA updated to add footnote "s" to indicate that additional imaging assessments can be performed at any time during the study, at the discretion of the investigator. 7. Table of contents updated to reflect clarifying section headers to enhance referencing and readability. 8. Section 1 Introduction: Added text to explain the unique risk of developing a Venous thromboembolic event (VTE) in neonates. 9. Section 1.2 Background and Rationale:

		updated to reorganize prior text to enhance readability by adding level 3 headings for Pharmacokinetics of Apixaban in Pediatric Subjects, Pediatric Formulation Development, Dose Selection Age Groups 1, 2, 3, and added new sub-section, Dose Selection for Age Group 4. 10. Section 1.2.4: updated Table 2 to include starting dose for neonates of both PK cohort and post-PK cohort. Added text to explain what happens with dosing when a subject reaches age 28 days or older. The Table 2 footnote c was updated accordingly. Added Table 2 footnote e, to indicate that if the PK sub-analysis determines that a different dose was necessary, a subsequent protocol amendment would be required. 11. Section 1.2.4: Dose Selection for Age Group 4. Added Area Under the Curve (AUC) ranges for reference. 12. Section 1.3.2: Potential Risks for Subjects. Statistics on subjects and patients treated with apixaban updated with current numbers. 13. Section 2.2 Endpoints: modified to clarify that endpoints would not be limited to Deep Vein Thrombosis (DVT) or Pulmonary Embolism) PE, and would include "other thrombotic events," as a component of the primary endpoint given that the most common category of VTE events in neonates is catheter related thrombosis and DVT or PE would be exceedingly rare events in neonates. This change is reflected elsewhere in the protocol for consistency. Other thrombotic events is also being added as a secondary endpoint. For consistency with the description of DVT, the secondary endpoint of PE is now described as symptomatic and asymptomatic PE. Other edits to endpoints section made to clarify the intent of all planned analyses.

		14. Section 3 Study Design: updated text to reflect that neonates would now be enrolled, including specification of their minimum weight and requirements for pre-treatment with standard of care, depending on whether the neonate was in the PK cohort or the post PK cohort. 15. Section 3 Study Design: There is a description of two categories of neonate subjects, those enrolled in the neonate PK sub-analysis, and those enrolled after completion of the PK sub-analysis. 16. Section 3 Study Design: updated to clarify when imaging should be performed, as described in the Schedule of Activities. 17. Section 4.1 Inclusion Criterion 1: updated text to clarify that neonates could now be enrolled, if they achieved a minimum weight of 2.6 kg. 18. Section 4.1 Inclusion Criterion 2: updated text to include central venous catheter-related thrombosis, as an example. 19. Section 4.1 Exclusion Criterion 1 updated to describe the pretreatment standard of care (SOC) requirements for both the PK cohort (a minimum of 5 and a maximum of 14 days prior to randomization) and the post PK cohort (may receive SOC for up to 14 days prior to randomization). 20. Section 4.2 Exclusion Criterion 12: Added the statement “or any of the other ingredients in the apixaban formulation, or hypersensitivity to any of the components of the comparators” to the exclusion on allergies to the study drug. 21. Section 5.2.2: sentence added “Neonates will only be administered 0.1 mg capsules with a minimum of 2.6 kg body weight.” 22. Section 6.2 Day 1, Screening Day, Physical

		exam, weight: a comment was added to reflect that a neonate subject's weight should be rechecked, when he/she reaches 28 days of age, at an unplanned visit. 23. Section 6.2.2 Study Period, Day 1, additional bullet added to state that for apixaban treated PK cohort neonates only, blood samples for PK assessment would be drawn, and that the details of that procedure would be provided in a separate reference document. 24. Section 6.2.4 Day 42: For Physical Examination bullet, added language "If there is a 20% change in weight for subjects less than 2 years old, the investigator may contact the study Sponsor to discuss a possible change in dosing regimen." 25. Section 6.4 Extension Phase. Edited to clarify that extension phase is only to be considered for subjects in age cohorts 1 through 3. 26. Section 6.7 Discontinuation of Subjects from Investigational Product: Added language to clarify what visits should be completed in the case of early discontinuation of treatment. 27. Section 7.2 Blood Volume Collection. Subsections 7.2.1 and 7.2.2 added and edited to distinguish between neonate blood volumes and those of older subjects. Dried blood spot sampling is also described, as an option to minimize the blood sampling volumes for the assessment of PK in neonates. 28. Section 7.2 Blood Volume Collection. Table 5 modified to distinguish between neonate blood volumes and those of older subjects. Footnote added to clarify the blood volume requirements for the screening labs. 29. Section 7.4.1 Pharmacokinetic and Pharmacodynamic Assessment, Sampling

		Time Points: Updated to describe specifications for neonate Day 1 PK analysis performed in neonates recruited prior to the completion of the neonate PK sub-analysis. 30. Section 7.8.1 Imaging Assessments: Sentence added reading, "Additional imaging assessments can be performed at the discretion of the Investigator at any time." 31. Section 9.4 Pharmacokinetic and Pharmacodynamic Analyses: Updated to describe PK sub-analysis to determine the neonate dose for Age Group 4. 32. Section 9.5 Interim Analysis: Updated to describe that an interim analysis of efficacy and safety will be performed for Age Groups 1 through 3, while Age Group 4 is still recruiting. 33. Section 9.6 Data Monitoring Committee: A statement was added to clarify that External Data Monitoring Committee may be provided with apixaban PK data, at its request. 34. Added reference for FRAGMIN® (dalteparin sodium) injection, for subcutaneous use Initial U.S. Approval in References section. 35. Appendix 2: Updated to include more current data on CV185118. 36. Added Appendix 5, which supplements Appendix 4, and describes dosing data for neonates. 37. Typographical or editorial changes applied globally.
Amendment 6	06 September 2019	1. Protocol Summary updated to reflect the summary of changes made throughout the protocol amendment.

		2. Updated Abbreviations Table. 3. Schedule of Activities, standard of Care may be administered up to 14 days prior to randomization. 4. Schedule of Activities, footnote regarding laboratory samples was updated to allow local labs to replace central labs to minimize blood volume collected in younger subjects. 5. Section 1: Introduction and Background update on pharmacokinetic data available to inform updated dosing as well as added information about 0.1 mg sprinkle capsule formulation of apixaban. 6. Section 1: Subjects enrolled in this study <2 years of age will be limited to SOC of only heparin (UFH or LMWH) due to the risk of the subject's inability to swallow VKA, manipulation of VKA locally, and limited use of VKA in this population. (recommended by BfArM and supported by Steering Committee). Any references to treatment with SOC VKA have therefore been removed from the Protocol. 7. Section 3: Language added to provide reader with a definition of "index event". 8. Section 3: Study Design updated to indicate closure of enrollment of Age Groups 1 and 2. Enrollment will be focused on Age Group 3 (28 days to <2 years). 9. Section 3: Study Design updated to allow flexibility of treatment duration of 6 to 12 weeks in subjects <2 years of age to support enrollment efforts. 10. Section 3: For subjects less than 2 years of age, the midpoint imaging is only required at the discretion of the investigator but an EOT image should be collected. 11. Section 4: Subject Selection criteria updated

		to enroll subjects <2 with the intent to treat of 6 to 12 weeks to support clinical practice and enrollment efforts of younger subjects. 12. Section 4: Subject Selection criteria updated with 4 exclusion criteria and 1 inclusion criterion to maintain program level consistency with regards to safety (exclusion of subjects with known or acquired APS, exclusion of subjects with a known or inherited bleeding disorder or coagulopathy, inability to tolerate oral feeding, and exclusion of ECMO/VAD subjects). 13. Section 5: Study treatments section updated to include 0.1 mg apixaban formulation, added instruction requiring contact to confirm subject/caregiver understanding of dosing instructions and noting in source, and removed home healthcare worker language. 14. Section 6: Study Procedures, updated to reflect all changes in SOA and treatment duration flexibility in subjects from birth up to <2 years of age. 15. Section 7: Assessments, updated to include details regarding adjudication of events referenced in Pfizer Adjudication Charter. 16. Section 9: Sample Size Determination, updated sample size from 150 to 250 with rationale included in update. 17. Typographical changes applied globally. 18. Added Appendix 4 which supplements Appendix 3 and describes dosing data for <2 years of age. 19. Updated References to include the 2018 ASH Guidelines.
Amendment 5	31 August 2018	1. Protocol Summary and Section 5 includes language restricting in Germany only the use of allowable Vitamin K Antagonist (VKA) formulations to be administered in pediatric

		subjects in accordance with local regulations. 2. Updated Benefit & Risk Section 1.3 [redacted]. 3. Added Section 7.2 Blood Volume Collection and Table 4 to provide an overview and table summarizing the maximum potential blood volume collected in pediatric subjects during study conduct [redacted] 4. Typographical changes were applied to Schedule of Activities, Protocol Summary, Section 5, Section 6 (addressed in Amendment 4 protocol administrative letter 12 Jan 2018). 5. References updated.
Amendment 4	30 October 2017	1. Title changed from Extrapolated to Descriptive Efficacy [redacted] 2. Updated Abbreviations Table. 3. Updated Protocol Summary to include information of palatability assessment for 0.5 mg tablet, revised dosing for apixaban & updated neonatal definition aligned with BMS protocol (Table 1), expansion of enrollment age down to 3 months of age, and dosing guidance in Appendix 3. 4. Schedule of Activities updated to include Extension Phase visits (Day 105, 126, 147, 168) and footnote "q" to differentiate 6-week vs 12-week extension visit procedures. 5. Schedule of Activities: Added table footnote "o" allowing first dose of apixaban to be administered at home to comply with waiting periods before first dose. 6. Schedule of Activities- Added table footnote "p" to clarify sites will be requested to continue the mg/kg dosing regimen for subjects who have been randomized and dosed using apixaban oral solution when

		Amendment 3 was effective (see Table 1). 7. Schedule of Activities updated to reflect palatability assessment for both formulations, 0.5-mg tablet and oral solution, of apixaban. 8. Added supplemental table to Schedule of Activities depicting procedures for subjects who continue on apixaban to "Extension Phase" (6-week or 12-week). 9. Table of Contents reflects the addition of Appendix 3. B0661037/CV 185-325 Dose Selection Rationale for Amendment 4. 10. Table of Contents reflects the addition of Table 6 added under List of Tables. 11. Table of Contents reflects the addition of Figure 3 under List of Figures. 12. Updated 1.2 Background and Rationale to include apixaban benefit/risk information. 13. Updated 1.2 Background and Rationale information on 0.5-mg apixaban tablets and formatting updated to include first mention of abbreviations (IB, USA, SC). 14. Updated Section 1.2 sub-heading "Clinical Experience with Apixaban in Pediatric Subjects" and updated heading title to "Pharmacokinetics of Apixaban in Pediatric Subjects". 15. Within Section 1.2, a new sub-section "Update on Pediatric Formulation" was included. 16. Updated Table 1 to reflect both the mg/kg dosing under Amendment 3 for subjects who are randomized and already dosed and fixed-dose, body weight-tiered regimen for subjects randomized or switched to 0.5-mg tablet under Amendment 4.

		17. Section 3 update: study enrollment will be open to subjects at least 3 months of age and ≥6 kg weight, Group 3 age changed to 28 days to <2 years; Group 4 neonates will be enrolled according to updated definition. 18. Section 4.1 updated inclusion criterion #1 to allow enrollment of children 3 months of age to <18 years of age at the time of consent. 19. Section 4.1 Inclusion criteria #6 updated [redacted]. 20. Section 4.3, Sentence 1 revised to clearly indicate that investigational product includes standard of care (SOC). 21. Section 4.3 updated to include definition of abstinence as defined in CT02 template. 22. Section 5.1 updated to specify neonate definition. 23. Section 5.2.1 added information on apixaban 0.5-mg tablets and European Medicines Agency (EMA) guidelines for [redacted] levels in oral pediatric products. 24. Section 5.2.2 updated first dose instructions for apixaban given at home and updated instruction for study drug administration of SOC/apixaban. 25. Section 5.2.4 updated to include information regarding visiting nurses in the study. 26. Section 6 updated for at-home administration of first-dose, palatability assessment for 0.5-mg tablet. 27. Section 6.2.6 Day 84 clarification note added indicating radiologic imaging that requires sedation or radiation at Day 42 visit is not required if not medically needed ([redacted]). 28. Added Section 6.4 Extension Phase study

		procedures. 29. Section 7.4 clarified prior medication and concomitant medication recording throughout study as indicated in the Schedule of Activities. 30. Section 7.5 Bleeding Assessments updated text to clarify requirements as defined by ISTH criteria for each category of bleeding. 31. Section 7.7 Palatability Assessments updated to include palatability assessment for 0.5-mg tablet. 32. Section 8.1.1 updated text to provide sites with additional guidance for SAE reporting to BMS or its designee. 33. Updated Appendix 2. 34. Added Appendix 3 "B0661037/CV185-325 Dose Selection Rationale for Amendment 4". 35. References updated.
Amendment 3	01 March 2017	1. Changed "Phase 4 (Phase 3 if required by local regulation)" on the cover page to "Phase 4 (Phase 2 or 3 if so designated by local regulation). 2. Updated Apixaban Doses for Age Groups 1 and 2. 3. Changed Follow-Up Period from "30±5 days post End of Treatment" to "35±5 days post End of Treatment" to remain compliant with current Pfizer and BMS SOPs. 4. Updated section on "Clinical Experience with Apixaban in Pediatric Subjects" with current information. 5. Updated inclusion criterion #1 to allow for enrollment of children 2 to <18 years of age at the time of consent (Age Groups 1 and 2).

		6. Corrected inclusion criterion #6 to be consistent with other parts of the protocol by requiring contraception use for at least 33 days (5 half-lives plus 30 days) after the last dose of assigned treatment. 7. Added clarifying text to Section 5.2.2 Preparation and Dispensing, to allow flexibility with timing of drug preparation. 8. Added text related to [redacted] apixaban tablet administration in Section 5.2.3 Administration. 9. Added additional instructions for subjects on Apixaban treatment who required apixaban beyond Day 84. 10. Updated the wording that relates to Potential Drug Induced Liver Injury (DILI) to be consistent across the apixaban pediatric program. 11. Added "Throughout the trial, the study team, in conjunction with regulators (ie, FDA), will evaluate exposure duration, imaging results, and other aspects of the trial to determine if the data from the subjects in the trial are sufficient to address the objectives of the trial. For example, safety will be evaluated over 12 weeks of exposure to apixaban. Throughout the trial, the Sponsor will monitor the number of subjects who do not complete 12 weeks of apixaban treatment and determine whether to recruit additional subjects to supplement the safety database, or not. A sample size increase cannot be determined a priori and will be based on careful consideration of the data from the trial." to Section 9.1 Sample Size Determination. 12. Updated the title for Appendix 1. 13. Added Appendix 2.

Amendment 2 (Country specific: Germany)	31 August 2015	1. Added to inclusion criterion #2, "**In Germany only**, cerebral sinovenous thrombosis will be excluded." 2. Added to exclusion criteria, "Cerebral sinovenous thrombosis **(in Germany only)**."
Amendment 1	20 July 2015	1. Changed "Phase 4" on the cover page to "Phase 4 (Phase 3 if required by local regulation)". 2. Updated Section 1.2 Background and Rationale. 3. Added the statement "An approved amended protocol will be implemented prior to enrollment of each subsequent age group." 4. Corrected examples of Index VTE status in Section 2.2. Endpoints from Index VTE status (eg, progression, regression, or resolution) to Index VTE status (eg, unchanged, regression, or resolution). 5. Added "Targeted physical examinations for evidence of bleeding will be performed at Day 14, 42, and 84 (EOT) visits and as clinically indicated." 6. Added visits on Days 28 and 63. Visit can be conducted by telephone or on site. 7. Added Day 84 (EOT) and "if not medically necessary" to the following statement: "Radiologic images that require sedation or radiation at the Day 42 or Day 84 (EOT) visits are not required and may be omitted, if not medically necessary." 8. Added "when medically appropriate" to the following statement: "In addition, when medically appropriate, new radiologic images will be obtained if recurrent VTE is suspected." 9. Limited Inclusion Criteria 1 to Age Group 1 only. "Children 12 to <18 years of age at the

		time of consent (Age Group 1). • An approved amended protocol will be implemented prior to enrollment of each subsequent age group (Age Groups 2, 3, and 4)." 10. Aligned the duration of contraception use (Section 4.3 Life Style Guidelines) with the duration of study exposure in the event of a pregnancy (Section 8.4 Pregnancy). 11. Updated Section 8: Adverse Events. 12. Updated Section 15.1 Communication of Results by Pfizer.
Original protocol	15 October 2014	Not Applicable (N/A)